TIMING, COUNTING

AND

CEREBELLUM.

A thesis

submitted in partial fulfilment

of the requirements for the degree

of

Doctor of Philosophy

in the

University of Canterbury

by

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University of Canterbury

1998

For Eugene

Contents

List of Figures

List of Tables

Acknowledgements

For their invaluable contribution to this thesis, I would like to gratefully acknowledge the following people: Dr. John Dalrymple-Alford for his tireless supervision, extraordinary commitment and warm friendship. Trish Meatchem for her technical support and expertise with the rats and for just being there. Nina Salm for her help with the histology in Chapter 3. My other friends and colleagues, Dr. Anthony Mclean, Graham Byatt, Mike Christie and Craig Webster for making level 6 such a stimulating and enjoyable workplace over the last 4 years. The technical and secretarial staff for all their help and assistance. Jenny Breukelaar for her advice, for constructive criticism, help with editing and unerring support. Finally, Jack and Isabella, thanks guys.

This research was supported by a University of Canterbury doctoral scholarship and a Neurological Foundation small projects grant.

Abstract

The present thesis employed psychophysical choice procedures to examine the role of the cerebellum in interval timing in Wistar rats within the context of W. H. Meck and R. M. Church's (1983) mode control model of timing and counting. Three competing hypotheses were examined: That the cerebellum functions as 1) an independent milliseconds timer; 2) part of an extended timing system where it contributes to scalar variance; and 3) part of an extended timing system where it contributes to constant rather than scalar variance. Counting was also evaluated as a way to examine a specific source of constant variance in timing. A review of the mode control model and sources of variance in counting and timing, together with consideration of the generalised Weber function, concluded that a single set of processes could accommodate performance across the milliseconds and seconds range timing as well as counting.

Lesions to the cerebellar hemispheres but not the cerebellar vermis produced some deficits in a millisecond discrimination task (200 to 800 ms) but discriminations in the seconds range (2 to 8 s) were unaffected by either type of lesion. In contrast, comparative lesions to nucleus accumbens produced deficits in both time ranges. Cerebellar hemisphere lesions but not vermal lesions also produced deficits in numerical discrimination. These findings suggest that damage to the cerebellar hemispheres influences a source of constant variability, because constant variability is a prominent source of error during millisecond timing but is masked by other sources of variability when timing longer durations (> 2 s). The deficits in numerical discrimination suggest that switch processes, a specific source of constant variance described by the mode control model, are disrupted by damage to the cerebellar hemispheres.

Prior to the lesion work, an extensive examination was also made of timing and numerical performance to establish that intact rats could discriminate the numerosity of trial unique signals which obviate concerns about non-numerical confounds. This work provided an unequivocal demonstration that rats can count sequential events, but they do so according to H. Davis and J. Memmott's (1983) "last resort" hypothesis.

Chapter 1

Introduction.

The psychological and neurobiological processes associated with timing and counting have engendered considerable interest in the recent literature (Church & Meck, 1984; Davis & Pérusse, 1988; Gallistel & Gelman, 1992; Gibbon, Malapani, Dale, & Gallistel, 1997; Ivry, 1996; Nichelli, 1993). In animals, timing is an important cognitive process that enables them to anticipate biologically significant events, and the neurobiological bases of timing have been the subject of extensive research (for reviews see Church & Meck, 1988; Meck, 1988, 1996, 1997). In contrast, the role of counting or counting-like processes in animal behaviour is less clear and although there have been many demonstrations of numerical discrimination in animals, little is known about the underlying neurobiology. Counting clearly provides the foundation for mathematical abilities in humans, and the study of the cognitive mechanisms underlying numerical discrimination in animals is important because it may provide the basis for counting in humans (Gallistel & Gelman, 1992). The proposal that timing and counting rely on a common underlying mechanism (Church & Meck, 1984; Meck & Church, 1983) provides the rationale for the current study of numerical discrimination and its relationship with timing and, together with recent evidence that cerebellar damage produces deficits in interval timing, provides the impetus for investigating cerebellar involvement in both counting and timing.

One important issue in the context of the present study is that the existence of counting in animals remains contentious (Davis, 1993; Davis & Pérusse, 1988; Thomas & Lorden, 1993) whereas the ability to time events is understood to be a fundamental attribute of animal behaviour (Gallistel, 1990). Some of the most convincing evidence that rats and pigeons can in fact count comes from an operant psychophysical choice procedure which has been used to develop an information processing model (Meck & Church, 1983; Church & Meck, 1984; Meck, Church, & Gibbon, 1985; Roberts & Mitchell, 1994; Roberts, Macuda, & Brodbeck, 1995) that satisfies

the accepted formal definition of counting (Gelman & Gallistel, 1978; Davis & Pérusse, 1988; Thomas & Lorden, 1993). However, the regular nature of the stimuli used in these studies raises concerns about the validity of their findings as demonstrations of animal counting. Specifically, an apparent numerical discrimination may have been supported by an unexpected temporal cue associated with stimulus pattern that covaries with number or, alternatively, it may have resulted from recognising the stimulus pattern itself. The main purpose of the first part of this thesis (Chapter 2) was to test rats' ability to count when presented with stimuli that obviate these major concerns. In addition, I examine whether counting is used only as a "last resort", in the absence of more salient cues (Davis, 1993; Davis & Bradford, 1986; Davis & Memmott, 1983; Davis & Pérusse, 1988), as opposed to a natural ability that animals routinely engage (Meck & Church, 1983; Capaldi & Miller, 1988).

The mode-control model of counting and timing developed by Meck and Church (1983) is an extension of an information processing model based on scalar timing theory[1] (Gibbon & Church, 1984) that provides an excellent qualitative and quantitative account of both human and animal timing performance. This model provides the conceptual framework for this thesis. After the empirical re-evaluation of the model in Chapter 2, the primary aim of the second part of the current research (Chapters 3 and 4) was to examine the contribution of the cerebellar cortex to processes that subserve counting and interval timing in rats. Deficits in the discrimination of brief durations by animals and humans with cerebellar damage has led to the leading hypothesis that the cerebellum provides an independent timing system, limited to the milliseconds range, for both perceptual (interval timing) and motor process domains (Keele, Pokorny, Corcos, & Ivry, 1985; Ivry, 1993, 1996). However, careful consideration of the theoretical aspects of timing under the mode-control model (Section 1.4) raises the possibility that the cerebellum plays a role in an extended information processing system, described by the model, that is responsible for timing in a range from millisecond to minutes. As we shall see, a quantitative analysis of the mode-control model also offers a rationale to study the cerebellum's contribution to this

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[1] This timing model is sometimes referred to as the scalar timing model (Church, 1984, Meck & Church, 1988), and sometimes as an information processing model of timing (Church & Gibbon, 1984). The nomenclature, mode-control model, of timing, or of counting and timing, subsumes all the features of the timing model which is more accurately a family of models, but their relative quantitative details are not relevant to the

information processing system through an examination of the effects of cerebellar lesions on counting in comparison with the effects of these lesions on timing in both the millisecond and seconds range.

Sections 1.1 and 1.2 provide a review of the empirical evidence for timing and counting that supports a description of the mode-control model, followed by a brief comparative discussion of two alternative models (Section 1.3). Gibbon's (1990) analysis of variance in timing is explained and this description provides the basis for the presentation of a similar analysis of variability in counting (Section 1.4). The subsequent sections review evidence for the neurological basis of the mode-control model (Section 1.5) and cerebellar involvement in timing (Section 1.6). Finally, Section 1.7 summarises the aims of the research reported in subsequent chapters.

1.1 The Nature of Animal Timing.

This section briefly reviews some of the experimental work with animals that provides the basis for the information processing model of timing and its development into the mode-control model of counting and timing. Most of the timing research has involved durations in the range from seconds to hours and very few studies have explored timing performance for intervals less than a second. The latter are also reviewed because of their relevance to the putative temporal domain of cerebellar timing and the formal analysis of the mode-control model described in Section 1.4. I begin by briefly describing the three main procedures used by Meck, Church, Gibbon and others in the studies of timing and counting by animals reviewed in this Chapter. However, only the psychophysical choice procedure was employed in the empirical work reported in this thesis.

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current discussion.

1.1.1 Animal timing procedures.

In the psychophysical choice or bisection procedure animals are reinforced for correctly choosing between two retractable levers (different colored key lights are used with pigeons) inserted into an operant chamber immediately following the offset of a either a long or short duration stimulus. The adaptation of this procedure to numerical discrimination (described in Section 1.2.2) has provided some of the most compelling evidence for a common basis between timing and counting in animals (Meck & Church, 1983; Meck, Church & Gibbon, 1985; Roberts & Mitchell, 1996). In timing studies, one of the levers is designated the long lever and responses to this lever are reinforced only after presentation of a long duration stimulus; the other lever is designated the short lever and responses to this lever are reinforced only after presentation of a short duration stimulus. Once the animals can accurately discriminate between this pair of standard durations, they are tested with probe signals that vary in duration between the standards and are usually unreinforced. The dependent variable is the probability of a response on one of the levers, usually the long lever (c.f. Gibbon, 1977), as a function of stimulus duration. This response probability gradient, approximately a cumulative normal distribution, represents the psychophysical function that provides several measures of timing performance (see Figure 1.1).

The difference limen (DL; Figure 1.1) is an estimate of just-noticeable-difference (JND) and is defined as the increment in stimulus magnitude (the comparison) that can be classified as different from a standard stimulus magnitude 50% of the time. In terms of discrimination training this has been described as the point, "half-way between no differential learning and complete learning, or simply, 75%" (Tarpy, 1969, p. 116). The stimulus magnitude at which the subject is equally likely to choose the standard or the comparison (50% or no differential learning) is known as the point of subjective equality (PSE). For the normal distribution, the PSE corresponds to the mean (μ), and the DL corresponds to 0.675 standard deviations ($DL = 0.675\sigma$), the point at which the larger area under the distribution is approximately 75% of the total area (Figure 1.1). The Weber fraction provides a normalized measure of sensitivity to

changes in stimulus magnitude and can be defined as DL/PSE (e.g., Church, Getty & Lerner, 1976; Meck & Church, 1983). This accepted definition is used throughout the present thesis, although it should be noted that some authors treat the coefficient of variation (σ/μ) as the Weber fraction by defining DL as equal to the standard deviation (DL = σ, e.g., Getty, 1975; Fetterman & Killeen, 1992). However, both definitions provide essentially the same measure of sensitivity to changes in stimulus magnitude. Overall performance can be measured by p(A), the

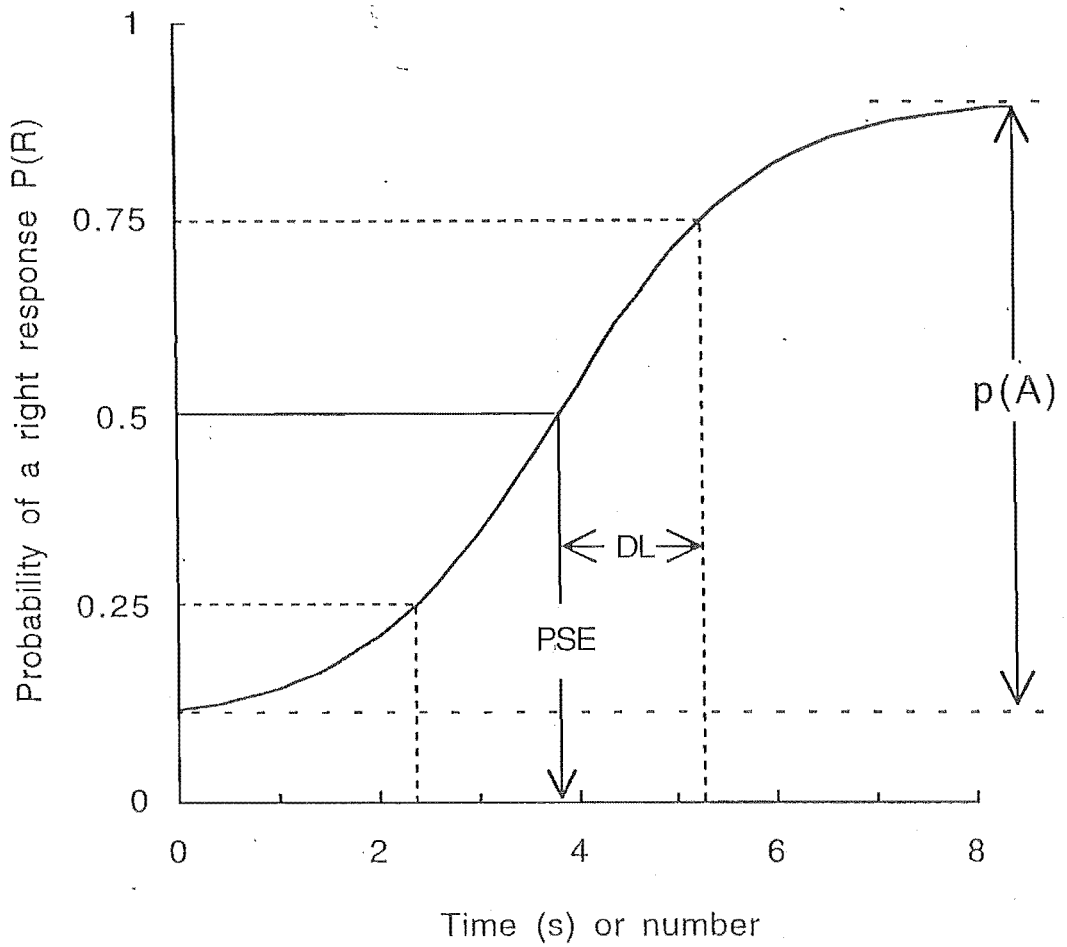

Figure 1.1. Illustration of the psychophysical function that describes performance during testing in the bisection procedure. The difference between the estimated asymptotes of the psychophysical function is p(A), a measure of overall performance (see Chapter 2, data analysis for details). The signal value at which either choice is equally likely is the point of subjective equality (PSE). The difference limen (DL) reflects the slope of the psychophysical function and is a measure sensitivity to changes in signal value.

probability that an animal will be correct when it attends to the stimulus. Inattention, p(~A) = 1-p(A), refers to any factor occurring on some trials only (ie. not on every trial) that results in an animal failing to base its choice on the relative stimulus dimension, *for any reason whatsoever* (Church et al, 1976; Heinemann & Chase, 1970).

The temporal generalization procedure is similar to the bisection procedure except that animals are reinforced after pressing a single lever inserted into the operant chamber following the presentation of the standard duration, usually with some form of limited hold (e.g., 5 s) after which the lever is retracted without reinforcement being delivered. Once presentation of the standard duration reliably elicits a response, the animals are tested with probe durations that vary in length around the standard (i.e., both longer and shorter). The dependent variable here is the probability of a response as a function of stimulus duration and the distribution generated over the range of probe durations, including the standard, is known as a temporal generalization gradient (Church & Gibbon, 1982).

The peak procedure is a discrete trial variant of the fixed interval (FI) schedules with intertrial intervals of 30 - 45 s, usually a blackout. A trial begins with the onset of a stimulus and reinforcement is delivered with the first response after some fixed interval and the stimulus is terminated (FI trails). On a proportion of the trials, known as peak trials, reinforcement is not available and the stimulus offset terminates the trial at some multiple (e.g., 3x) of the fixed interval. Responding is characterised on each trial by a low rate initially that abruptly changes to a high rate at the "break point" (Schneider, 1969) approximately 1/3 of the way into the fixed interval. On peak trials, high rate responding abruptly drops back to a low rate at some point, the "giving up time" (Brunner, Kacelnik, & Gibbon, 1992), after the point when reinforcement is usually made available. The dependent variable is response rate, usually normalized by the maximum response rate which is close to the time that reinforcement is available. The mean response rate distribution provides a measure of the maximum response rate known as the peak rate and the time of peak rate known as the peak time (e.g., Meck & Church, 1984; Roberts, 1981); individual trials also provide several measures of timing performance, the start and stop break points, the middle of this interval and its spread (Church, Meck, and Gibbon, 1994).

1.1.2 The scalar property and variability in interval timing: the seconds range.

The ubiquitous property of interval timing in the range from seconds to minutes is the superposition[2] of response distributions in relative time and a constant Weber fraction, attributes that Gibbon (1991) describes as "the hallmarks of scalar timing" (p. 6). For example, using the bisection procedure, Church and Deluty (1977) obtained psychophysical functions for rats over four different time ranges, 1 s to 4 s, 2 s to 8 s, 3 s to 12 s and 4 s to 16 s and these superposed when plotted in relative time (Fig 1.2A). Similar results have been obtained with human subjects tested with different pairs of standard durations in the range between 0.75 s and 3.6 s (Allan & Gibbon, 1991, Fig 1.2B). The similarity shown between human and animal timing is striking although it is important to note that studies with humans have tended to use short durations that preclude the use of chronometric counting (e.g., 1 Mississippi, 2 Mississippi, ...) as an aid to timing. However, a recent bisection study has shown that psychophysical functions superpose for humans tested over 1 s to 4 s and 2 s to 8 s when chronometric counting was suppressed by requiring subjects to read randomly displayed numbers out loud during the discrimination task (Wearden, Rogers & Thomas, 1997). Superposition has also been demonstrated with target durations of 2 s and 8 s for the temporal generalization procedure with rats and pigeons (e.g., Church & Gibbon, 1982) and in humans for several standard values over a similar time range (2 s to 8 s, Wearden, Denovan, Fahkhri, & Haworth, 1997). The scalar property has also been demonstrated for the peak procedure for durations ranging from 15 s to 60 s in rats and pigeons (e.g., Church, Meck, & Gibbon, 1994, Gibbon & Church, 1990, 1992).

Superposition is a consequence of timing processes where variance increases with the square of the mean (i.e, $\sigma^2 = k\mu^2$) or, alternatively, standard deviation is proportional to the mean. This is known as the scalar property and results in a constant Weber fraction ($0.675\sigma/\mu$).

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[2] Superpose is synonymous with superimpose and the former is used by Gibbon and his colleagues so I follow that convention here.

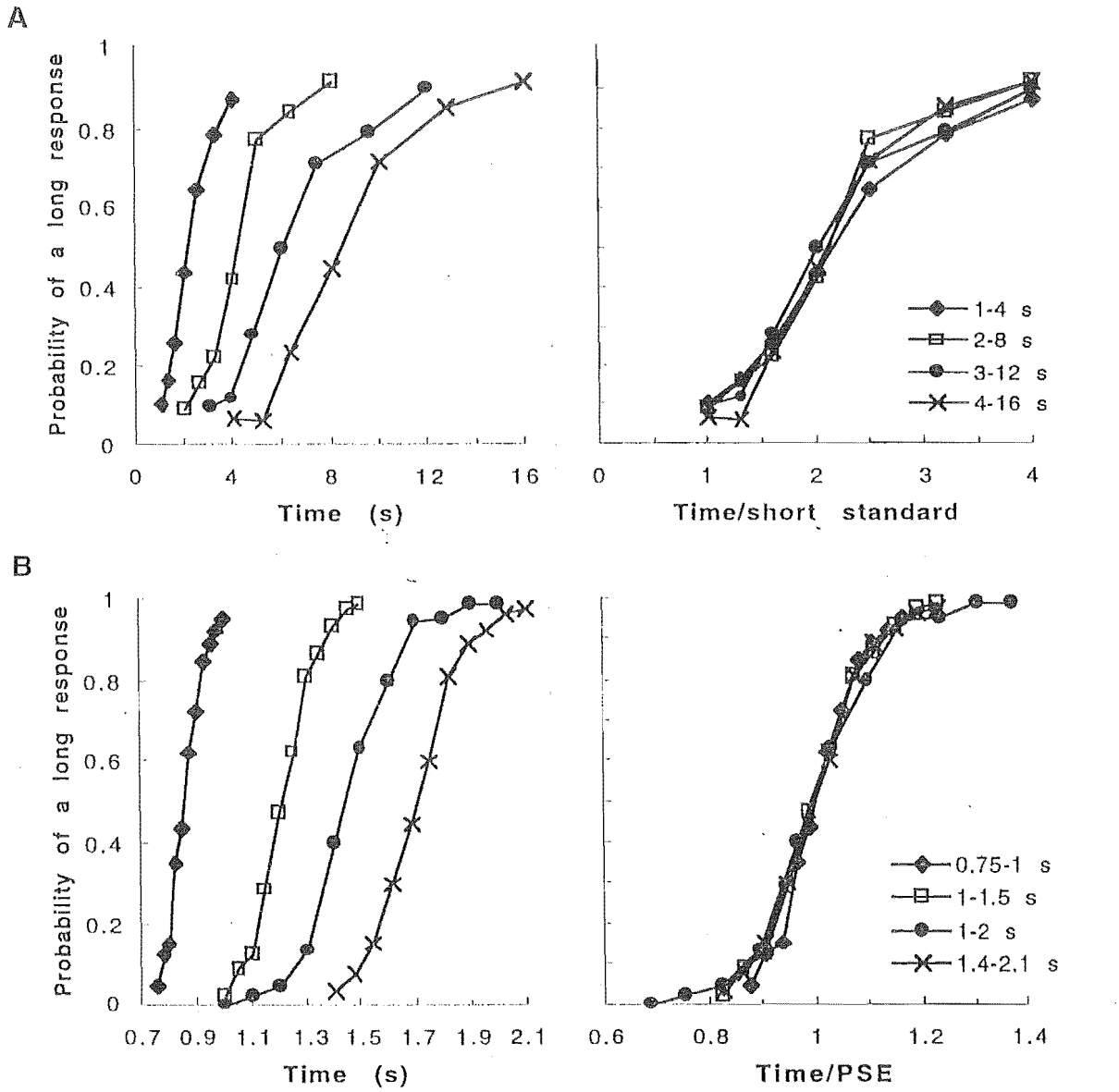

Figure 1.2. Panel A: Rats data showing the probability of a long response as a function of real time (left panel) and relative to the short standard (right panel). Mean data replotted from Church & Deluty (1977). Panel B: Human data showing the probability of a long response as a function of real time (left panel) and relative to PSEs (right panel). Mean data replotted from Allan & Gibbon (1991).

In the bisection procedure, superposition, in real time, appears to require a constant ratio between standards for each time range (Allan & Gibbon, 1991; Church & Deluty, 1977; Wearden et al, 1997). For example, in Figure 1.2A the ratio of the standards (or ratio of the extremes) is 1:4 for all time ranges and these functions superpose when normalized relative to the short standard. However, when ratios of the standards differ, as they do in Figure 1.2B, superposition is only obtained when the functions are plotted relative to the PSE (Allan & Gibbon, 1991). This important constraint reflects the fact that the scalar property operates on

subjective time because the latter produces superposition irrespective of the ratio of the standards. Psychophysical functions plotted relative to the PSE superpose for all ratios between standards (Allan and Gibbon, 1991; Gibbon, 1986) although an exception was reported by Allan and Gibbon (1991) between 4 and 6 s, the longest durations used, where the Weber fraction was larger than for all other conditions. There have also been some other reports of increasing Weber fractions at longer time ranges for humans (> 2.5s, Getty, 1975, see Figure 1.3A, left panel) and pigeons (> 10 s, Zeiler, 1991).

The scalar property has been particularly important to the development of the information processing model of animal timing as it restricts the types of variance that are admissible in a formal quantitative description of timing, as described in Section 1.4. However, there is some evidence, discussed below, that the scalar property fails (i.e., Weber fractions increase) for rats with durations less than 1 s and for humans and pigeons with durations less than 0.25 s.

1.1.3 The scalar property and variability in interval timing: the milliseconds range.

Most studies of human timing have been restricted to relatively short durations but there have been very few parametric psychophysical studies with animals for durations less than 1 s (Fetterman & Killeen, 1992). In humans, response distributions superpose for the bisection procedure between 0.1 and 0.9 s (Wearden & Ferrara, 1996), the temporal generalization procedure for target intervals of 0.5, 0.6 and 0.7 s (Wearden, 1992) and the peak procedure for target intervals of 0.5, 0.7, 0.9, 1.1 and 1.3 s (Wearden & McShane, 1988). By comparison, only 4 parametric studies have examined temporal discrimination in animals for the milliseconds range. Two studies with pigeons have shown that between 0.25 and 1.0 s the Weber fraction is constant (Yamashita, 1986; Zeiler, 1991), although it should be noted that when Zeiler's (1991) birds were not food deprived, their Weber fractions increased as durations became shorter within this range. The remaining two studies, one with pigeons and the other with rats (Church, Getty & Lerner, 1976; Fetterman & Killeen, 1992), showed that Weber fractions increased at some

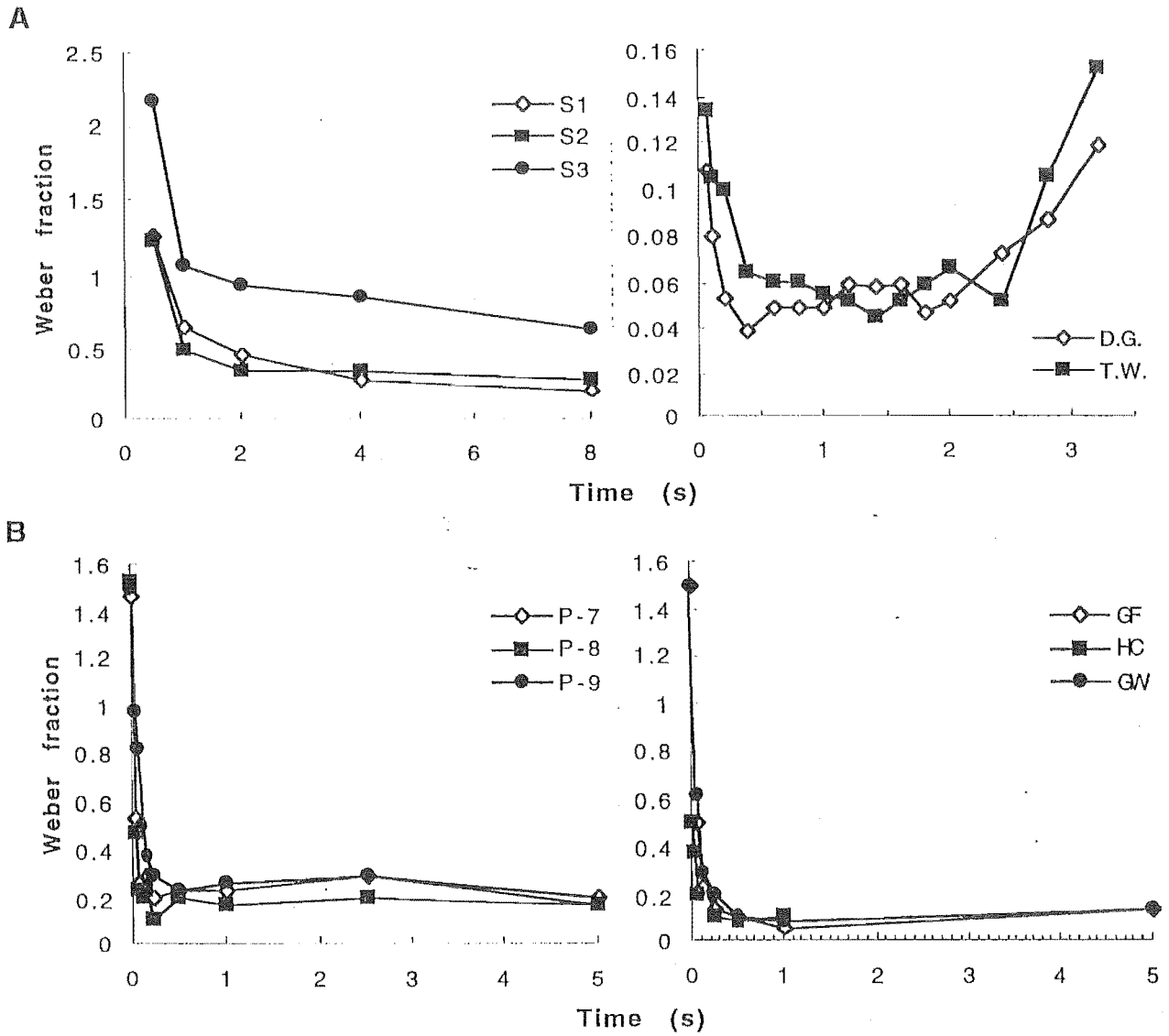

Figure 1.3. Panel A: Weber fractions as a function of the short standard for rats (left panel, data replotted from Church et al, 1976) and for humans (right panel, data replotted from Getty, 1975). Panel B: Weber fractions as a function of the short standard for pigeons (left panel) and for humans (right panel). Data replotted from Fetterman & Killeen, (Experiment 1, 1992).

point as the test stimuli became shorter and are of particular interest because these data from animals are directly comparable to data obtained from humans using analogous procedures.

The procedure used by Church et al (1976) was similar to the bisection procedure described in Section 1.1.1 except that during testing the short standard was held constant while the long duration was continually adjusted until the probability of a long response was 0.75 (a "staircase" method). The difference between the long duration obtained in this way and the short standard provided an estimate of the DL for different values of the short standard that ranged between 0.5

to 8 s. Figure 1.3A (left panel) shows the mean Weber fraction plotted as a function of the short standard for the data collected by Church et al (1976) and it is readily apparent that although the Weber fraction is relatively constant for durations greater than 2 s, the rats sensitivity to time rapidly decreases for durations less than 2 s. These results are similar to those obtained earlier by Getty (1975, Figure 1.3A, right panel) using an analogous procedure with 2 highly trained humans in the range from 0 to 2.0 s although the increase in Weber fraction occurs at durations almost an order of magnitude shorter than that found for the rats (Church et al, 1976).

Getty (1975) developed a generalization of Weber's law that provides a good description of the rising Weber fraction found at very short durations with the humans and in the later study with rats (Church et al, 1976). Weber's law is a psychophysical generalization which states that JNDs in stimuli are proportional to the magnitude of the standard stimuli. Formally, for time,

$$\Delta t/t = k, \tag{1.1}$$

where k is the constant. The generalization of this law (Equation 1.2) is based on an explanation that attributes the rise in Weber fraction to a sensory noise component that is always present irrespective of stimulus duration. Getty (1975) assumes that overall variability in a discrimination task arises from several sources of variability, both those dependent and those not dependent on the stimulus magnitude. If these two types of variance are mutually independent, then all magnitude dependent variance can be combined in one component, $V(t)$, and all magnitude independent variance can be combined into a constant residual component, $V(r) = c$. Assuming that $V(t)$ obeys Weber's law (i.e., $V[t] = [kt]^2$), Getty derives the following form of the generalised Weber's law for total variance, Var(t):

$$\mathrm{Var}(t) = (kt)^2 + c, \tag{1.2a}$$

and

$$\mathrm{SD}(t) = ([kt]^2 + c)^{0.5}, \tag{1.2b}$$

where k and c are constants.

For DL = 0.675σ, the generalised form of the Weber fraction is given by,

$$\mathrm{DL}/t = 0.675(k^2 + c/t^2)^{0.5}, \tag{1.3}$$

and it is clear that as t increases the Weber fraction decreases rapidly towards an asymptotic value of $0.675k$. For both rats and humans (Church et al, 1976; Getty, 1975), the generalised form of the Weber fraction gave an excellent description data that was also superior to an alternative model of variability in timing where magnitude dependent variance is assumed to be proportional to time ($V[t] = kt$, Creelman, 1962).

Recently, Fetterman and Killeen (1992) used the same procedure as Church et al (1976) to evaluate the ability of pigeons and humans to discriminate between brief durations ranging from 0.05 to 5 s but with most durations below 1 s. Pigeons were also tested with a standard bisection procedure over 3 conditions with standard durations of 0.05 and 0.10 s, 0.5 and 1 s, and 5 and 10 s. The results from both experiments with pigeons showed that the Weber fraction remained constant over most of the time range tested before rising rapidly for durations less than about 0.25 s (Figure 1.3B, left panel). These findings are consistent with other evidence that the Weber fraction for pigeons is constant between 0.25 s and 1 s (Yamashita, 1986; Zeiler, 1991). The data for human subjects took a similar form (Figure 1.3B, right panel) although the humans showed greater temporal acuity overall than the pigeons but both data sets were equally well described by the generalised form of the Weber function (Equation 1.3).

It is interesting to note, however, that although the asymptotic Weber fractions for the pigeon (Fetterman & Killeen, 1992) and rat (Church et al, 1976) data are similar, the residual or constant variance is almost an order of magnitude higher for rats compared with pigeons even though the procedures were the same. This may be an important factor when trying to establish realistic estimates for parameters in the components of the information processing model of interval timing described in later sections.

In summary, according to the scalar property, standard deviation or difference limen is proportional to subjective time. The property appears to hold for animals in the range from seconds to minutes. In the milliseconds range, however, constant or residual sources of variance begin to have a greater impact on overall variance and the scalar property fails at very short durations. The scalar property has important consequences for the development of a quantitative description of the information processing model described in the next section although, as we will see later, this formal model can also account for the increase in Weber

fraction when durations become very short. However, the success of the generalised Weber's function provides evidence that a single model might describe interval timing in animals over a broad time range from the threshold of timing to minutes. This same model may also apply to humans, at least up to the point where cognitive processes not shared by other animals, such as language, provide alternative timing strategies.

1.2 The Mode-control Model of Counting and Timing.

1.2.1 The mode-control model of timing.

This information processing model of timing (Church and Gibbon, 1984) is an elaboration of earlier clock-counter models of interval timing (Creelman, 1962; Treisman, 1963). These models are described by three information processing stages: a clock stage, a memory stage and a decision stage (Figure 1.4). The clock stage consists of a pacemaker and an accumulator which, in its broadest sense, can be any process which records change over time from an arbitrary starting point. The memory stage provides a store for this information (temporary and permanent), presumably when it is associated with significant events. The decision stage initiates appropriate behaviour on the basis of stored and current temporal information. All three stages are treated as internal processes by the information processing model of timing although this need not be the case. For example, the behavioural theory of timing (BeT, Killeen & Fetterman, 1988) is an alternative model that treats the memory and decision stages as behavioural states, driven by an internal clock. These behavioural states rather than internal representations provide the basis for temporal discrimination and the decision stage is simply the end of a chain of behaviour. BeT and its value as a heuristic to investigate the neurobiological basis of timing are considered in more detail in Section 1.3.2.

In the mode-control model of timing the clock stage is assumed to consist of a Poisson pacemaker that generates pulses at a relatively high rate which can be switched to an accumulator

(the counter) that records the number of pulses over a given period of time. The pacemaker rate has not been established for animals, although in humans it has been estimated at approximately 50 Hz (Treisman, Faulkner, Naish, and Brogan, 1990). Pacemaker rate is sensitive to levels of the neurotransmitter dopamine (DA). The dopaminergic agonist, methamphetamine, and antagonist, haloperidol, respectively, increase and decrease pacemaker rate in rats (Meck, 1983). Dopaminergic drugs also influence the acuity of temporal discrimination in humans although the direct effects of these drugs on pacemaker rate have not been measured (Rammsayer, 1997; Rammsayer & Vogel, 1992).

Other details of the clock stage have been implied through the remarkable flexibility that animals demonstrate in temporal discrimination. For example, rats can abstract temporal attributes across modalities, a finding which supports the notion that timing is a central process (Meck & Church, 1982). Animals also appear to be able to simultaneously time up to at least 3 durations (Meck & Church, 1984; Leak & Gibbon, 1995) and can interrupt timing during "gaps" in a signal (Meck, Church & Olton, 1984; Roberts & Church, 1978, Roberts, 1981). These findings suggest that multiple switch-accumulator mechanisms operate in parallel and in different modes. For interval timing two modes have been proposed, the run and stop modes (Figure 1.4). In the run mode, the switch closes[3] at the onset of a timed stimulus and reopens at its termination and the accumulator is reset before any subsequent operation of the switch. By contrast, the stop mode explains interval timing across gaps in a signal and in this mode accumulator values are retained with each switch operation to produce a cumulative record of the durations of discrete events. For example, if two events with durations of e_1 and e_2 s are separated by an interval of i s, the quantity of pulses accumulated in the run mode, given a pacemaker rate of λ, would be $\lambda(e_1 + e_2 + i)$ whereas the quantity of pulses accumulated in the stop mode would be $\lambda(e_1 + e_2)$.

The memory stage of the information processing model consists of a working memory into which current accumulator values are transferred and reference memory which contains a distribution of accumulator values associated with significant events, for example stimulus

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[3] As with an electrical circuit a closed switch completes the circuit allowing pulses to flow into the accumulator. When the switch is open the circuit is broken and pulses cannot be accumulated.

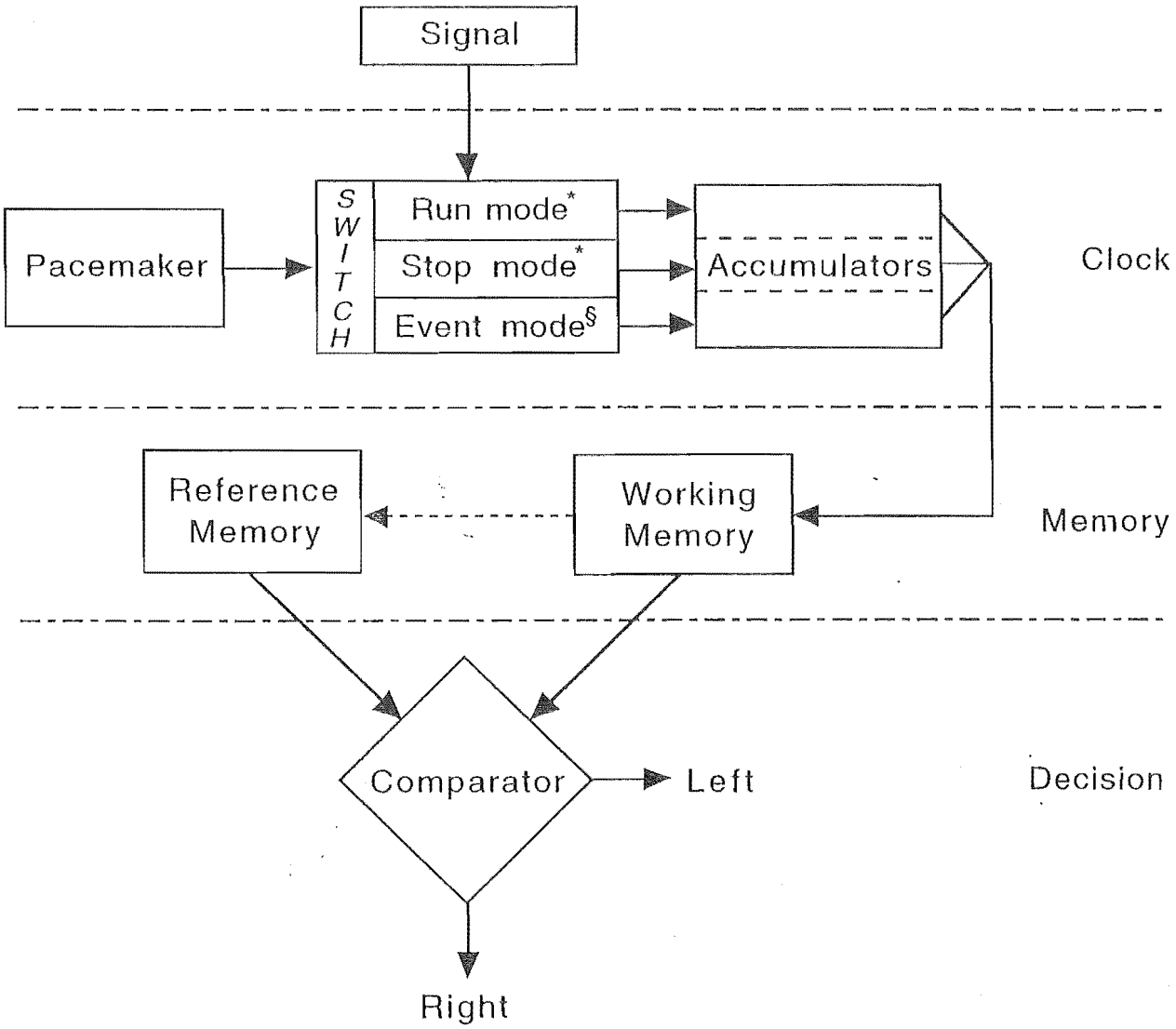

Figure 1.4. Components of an information processing model of interval timing and counting (After Meck et al, 1985). An * indicates a timing mode and a § indicates counting mode.

durations associated with reinforcement. In many timing tasks, working memory may be a redundant feature (an exception might be delayed-matching-to-sample tasks) because it simply replicates accumulator function (Gibbon, 1991). At the decision stage, ratios between the current accumulator values and samples drawn from reference memory are compared to a response criterion the outcome of which determines the animal's behaviour depending on the context, for example, whether to choose the right or left lever in a temporal bisection task (Figure 1.4). The details of memory and decision stages have been inferred primarily from the analysis of sources of variability within the information processing model that comply with the scalar

property (e.g., Gibbon & Church, 1984) and the role of the neurotransmitter acetylcholine (ACh) which appears to influence the magnitude of the remembered duration (Meck, 1983). The role of both ACh and DA in temporal discrimination is discussed further in Section 1.5.

Several studies, then, have shown that animals can use the various temporal attributes of a sequence of events, such as sequence duration, event duration or the sum of event durations as discriminative cue and the information processing model of timing provides a theoretical description of the underlying mechanisms.

1.2.2 Animal counting and its relationship to timing.

Number is another attribute of an event sequence that may provide animals with an important discriminative cue. The problem of confounding non-numerical cues, however, has made the demonstration of numerical competence in animals controversial (see Davis & Memmott, 1982; Davis & Pérusse, 1988 and commentaries; Thomas & Lorden, 1993) and is an issue which I address in detail in Chapter 2. Fernandes and Church (1982) have shown that rats can discriminate between two and four sequential events while temporal cues, such as event and interevent duration, were counterbalanced across number and other temporal cues, such as total sequence duration, were held constant. The seminal study in this area, however, is that of Meck and Church (1983) who examined how readily rats will use these numerical cues and the relationship between timing and counting.

The purpose of Meck and Church's (1983) study was to investigate the possibility that rats might be able to process temporal and numerical information simultaneously but independently, and "to determine whether or not the same mechanism is used for the discrimination of the number of sequential events and duration" (p. 320). They trained rats using a psychophysical choice procedure with compound standards where both time and number indicated the correct lever choice; after a compound two-event, 2 s (2e/2s) signal a response on the designated few/short lever was reinforced and after a compound eight-event, 8 s (8e/8s) signal a response on the designated many/long lever was reinforced. These signals consisted of a sequence of

white noise events for which event and interevent durations were equal. Total duration of these event sequences was the relevant temporal attribute and number of events was the relevant numerical attribute. Once the rats had successfully acquired this discrimination, relative control of choice behaviour by time and number was tested with two types of unreinforced probe signal. Control by time was tested by fixing the number of events at the geometric mean of the two training values (4 events) while total duration varied between the standard durations used during training (time relevant probe signals, 4e/2s, 4e/3s, 4e/4s, 4e/5s, 4e/6s, and 4e/8s). Control by number was tested by holding total duration fixed at the geometric mean of the two training values (4 s) while number of events varied between the number of events used during training (number-relevant probe signals, 2e/4s, 3e/4s, 4e/4s, 5e/4s, 6e/4s, and 8e/4s). Their principal finding was that the psychophysical functions generated by these probe signals superposed, indicating strong yet independent control of choice behaviour by both time and number.

In a second experiment of the Meck and Church's (1983) study separate pairs of time and number standards were used during training because steady-state performance could not be maintained during testing when compound standards were used as the training stimuli. Methamphetamine administered immediately prior to testing in this experiment moved the psychophysical functions generated for time and number by a similar degree to the left (approximately 10%), an effect that was interpreted as an increase in the speed of a pacemaker underlying both timing and counting performance. Another experiment showed that the amount of cross-modal transfer from auditory to cutaneous signals was also found to be the same for time and number.

These similarities between temporal and numerical discrimination provide support for the proposal that a single internal mechanism is used for timing and counting. Even stronger evidence comes from a measurable quantitative equivalence between number and time (Meck & Church, 1983; Meck, Church, & Gibbon, 1985). For example, Meck et al (1985) trained rats to press a lever designated short after 1 s of continuous white noise and a lever designated long after 2 s of continuous white noise and then tested the rats with unreinforced intermediate durations to generate a psychophysical function for time. The rats were also tested with two types of event sequence consisting of either a series 0.5s sound-on and 0.5s sound-off cycles or

a series 1.0 s sound-on and 1.0 s sound-off cycles and in which the number of cycles for each type of sequence varied between 5 and 10. The same smooth curve described the test data from continuous signals and the two types of segmented signal, irrespective of cycle duration, suggesting a quantitative relationship between timing and counting sequential events (i.e., 5 counts = 1 s).

Within the context of the information processing model of timing, the number of pulses accumulated during each "count" thus appeared to be equivalent to that accumulated during 0.2 s of continuous signal. To accommodate this finding, a third switching-mode, the event mode (see Figure 1.4), was proposed for the information processing model (Meck & Church, 1983; Meck, Church, & Gibbon, 1985). The event mode is similar to the stop mode with the critical difference being that in the event mode switch closure at the onset of each event immediately triggers reopening of the switch. There is, however, a small latency ($t_2 \approx 0.2$ s; Figure 1.5) between switch closure and reopening that allows a relatively fixed quantity of pulses to be passed to the accumulator. As in the stop mode, accumulator values are retained after each switch operation so that following a sequence of events the total quantity of pulses accumulated is proportional to the number of events in the sequence. For example, if a sequence of n events with durations $e_1, e_2, \ldots e_n$ and interevent intervals of $i_1, i_2, \ldots i_n$ is presented, then the following quantities (m) will be accumulated with a pacemaker rate of λ; in the run mode, $m = \lambda\Sigma\ (e_j + i_j)$ representing the total duration of the sequence; in the stop mode, $m = \lambda\Sigma(e_j)$ representing the cumulative duration of all events; and in the event mode, $m = \lambda n t_2$ representing

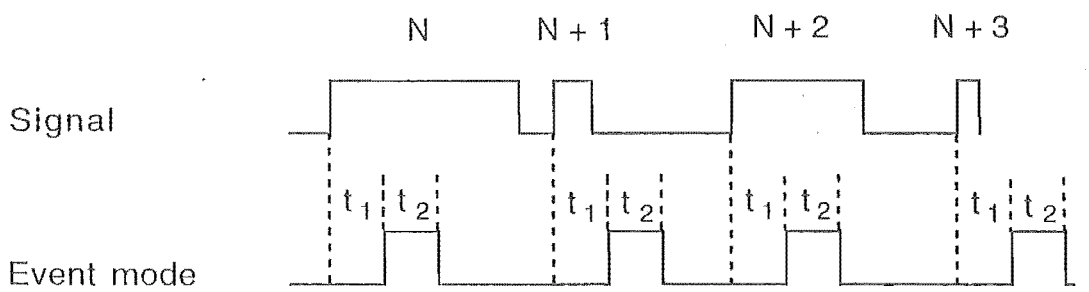

Figure 1.5. Switch operation in the event mode of the mode-control model of timing and counting (Meck & Church, 1983) during the counting of sequential events.

the total number of events. Because the values for λ and t_2 are relatively stable from trial to trial, m is proportional to n.

An alternative explanation of Meck, Church, & Gibbon's (1985) results is based on a quantal analysis of timing in humans (Kristofferson, 1984). In this view, the run mode accumulates bursts of pulses 200 ms apart and the event mode accumulates a single burst of pulses following each event. However, amphetamine cannot effect the interburst interval and must increase the number of pulses per burst to produce the same shift in time and number curves. This quantal hypothesis also means that to accurately time durations less than 1 s interpulse intervals must be progressively halved suggesting discontinuities in timing performance that have not been demonstrated in non-human animals.

An important feature of the event mode is that it meets the three basic criteria of the accepted formal definition of counting (Broadbent, Ratikin, Church, and Meck, 1993; Davis & Pérusse, 1988; Gelman & Gallistel, 1978).

> Criterion 1: the one-one principle. The current accumulator value is applied to each event in a one-to one-correspondence.
>
> Criterion 2: the stable-order principle. The quantity of pulses accumulated are reliably ordered because the accumulator value increments by a relatively fixed amount for each count.
>
> Criterion 3: the cardinal principle. The final value in the accumulator is a unique value which can be considered a tag that describes the numerosity of the entire event sequence.

As a consequence, the numerical discrimination of sequential events by animals can be properly described as counting but the event mode or a similar mechanism is critical to this description.

Recently, Roberts and Mitchell (1994) used the bisection procedure to train naive pigeons in a discrimination between different coloured keys where both the numerosity and duration of compound standards (2e/2s and 8e/8s) predicted the correct key choice. The procedure was similar to Meck and Church's Experiment 1 (1983) except that in the pigeon study a houselight served as the event stimulus, event duration was fixed at 200 ms for all signals with interevent

intervals determined by the total duration, and number of events and all probe signals were reinforced irrespective of key choice. Roberts and Mitchell (1994) claimed that the results of their experiment "clearly replicate those of Meck & Church's [Experiment 1] (1983)" (p. 68). In fact, their psychophysical functions for time and number did not superpose. In the pigeon study, performance with the 8e/4s probe signal was only at chance, plus the pigeons were far less likely to choose the few/short key after the 2e/4 s probe signal than the 4e/2s probe signal (77.5% compared with 90.4%, for two events [2e/4 s] and 2 s [4e/2s] respectively). In their second experiment, Roberts and Mitchell (1994) explicitly trained the same pigeons to treat total duration as an irrelevant stimulus attribute and to base response choice solely on number of events (i.e., the two-event and eight-event standards were 2e/2s, 2e/4s, 2e/8s, and 8e/2s, 8e/4s, and 8e/8s, respectively). Not surprisingly, when these pigeons were returned to the initial training (compound standards, 2e/2s and 8e/8s) and testing procedures, the psychophysical functions showed that number had gained stronger control of choice behaviour than time (Experiment 3). However, in the remaining two experiments, Roberts and Mitchell did show that pigeons could use post-sequence cues to selectively retrieve either numerical or temporal information to guide response choice. To account for these latter findings, they proposed that the mode-control model should be modified so that temporal and numerical information is passed to separate locations in working memory where it can be accessed separately and preferentially on the basis of past learning.

Both Meck and Church (1983) and Roberts and Mitchell (1994) claim that their results show that rats and pigeons can simultaneously process temporal and numerical information. Meck and Church's (1983) findings certainly appear to support the claim that "...it is not necessary to train animals to count or to time; they are able to do this *naturally*, and although we observe them to be timing, they may also be counting and vice versa" (p. 330, italics added). However, Roberts and Mitchell's (1994) results do not support this claim. Their pigeons were explicitly trained to ignore the temporal attributes of sequences and to attend to numerical attributes of the sequences before showing strong control of choice by number. Roberts and Mitchell's (1994) data raise questions about the natural utility of number to animals, an important issue that is addressed in Chapter 2.

1.3 Alternative Models of Timing and Counting.

1.3.1 A connectionist model.

A connectionist model of interval timing has recently been developed by Church and Broadbent (1990) which they propose may be more representative of the nervous system than previous models. The main components of the connectionist model are similar to those of the mode-control model - a clock stage, a memory stage and a decision stage - but are implemented differently. The essential difference between the two models is that the mode-control model's pacemaker-accumulator mechanism is replaced by two sets of tightly coupled oscillators and associated status indicators. The result is an extended timing system where as few as 11 oscillators provide a timing range from 200 ms to over 3 years when the ratio of adjacent oscillators is 2:1. During interval timing the oscillators, or a subset of the oscillators relevant to the time range of the particular timing task, are reset (i.e., entrained by the stimuli) at the start of each timing trial. Each status indicator records the half phase of its oscillator so that the set of status indicators provides a storage vector with the phase of each oscillator encoded as either +1 or -1. An additional element was added to this vector to encode the status of reinforcement; +1 or -1 for reinforcement and non-reinforcement and 0 when the status of reinforcement is unknown (e.g., before the trial outcome is known).

The memory components of the connectionist model are instantiated as auto-association matrices so that temporal information is explicitly stored in a distributed form. This type of temporal memory which represents the strength of connections within a neural network may be more plausible, neurobiologically, than the sampling distribution that forms the basis of reference memory in the mode-control model. Working memory is an autoassociation matrix of connection weights (-1, 0, or 1) representing the correlation of each element in the status indicator vector with all the other elements of the vector except itself (set to zero because elements are assumed not to be connected to themselves). This working memory matrix is calculated through the outer product of the status indicator vector and its transpose. The contents

of working memory are combined with reference memory by a linear operator rule; for example with a learning rate parameter of 0.01 a 1% weighting of the working memory matrix is combined with a 99% weighting of the reference memory matrix (e.g., Broadbent & Church, 1990). The retrieval oscillator - status indicator set is identical to those used for storage and this duplicate set was included in the model so that independent variables might have different effects on storage and retrieval processes. The elements of the retrieval oscillator - status indicator set are known as the retrieval vector which is multiplied with reference memory to produce an output vector. The output vector is then compared with the original retrieval vector through computation of the cosine of the angle between the vectors. This similarity measure, s, the inner product of the two vectors normalized by their length,

$$s = r^T o / [(r^T r)(o^T o)]^{0.5} \qquad (1.4)$$

where r and o are the retrieval and output vectors, respectively, and the superscript ^{T} indicates the transpose of a vector, is compared to a response criterion. The comparison process takes the form of a ratio rule as it does in the mode-control model (Section 1.4.1 provides a formal description of these rules).

Simulations of the peak procedure and fixed interval responding using the connectionist model have shown that there are many similarities between these data and experimental findings. Response probability distributions within single trials and across many trials usually took the same form as the experimental data and superposed in relative time (Church & Broadbent, 1990, 1991; Wearden & Doherty, 1994) although some systematic deviations are also to be found. However, it should be noted that superposition is not an emergent property but is built into the model through the method of introducing variability into the oscillators. This is done through adjusting the period of each oscillator on every trial by multiplying the mean period by a single random variable drawn from a normal distribution with a mean of 1.0 and a standard deviation that was constant across oscillators and trials. In effect, oscillator variance is determined by multiplying the period of each oscillator by a constant.

The connectionist model should also be able to account for the relationship between timing and counting and two alternative mechanisms have been proposed (Church & Broadbent, 1990, 1991). First, the connectionist model could incorporate an event mode analogous to the one

described for the mode-control model although it may not be entirely plausible that oscillators run for a short period and are then reset for each event (Broadbent, Church, Meck, & Rakitin, 1993), particularly if numerical and temporal information needs to be processed simultaneously. However, a solution to this problem may be to use a subset of oscillators with periods less than 200 ms in an event mode. Second, number might be represented as a relationship between durations such as a temporal ratio (Church & Broadbent, 1990). For example, when a fixed number of events occur at regular intervals, the ratio of interevent duration to total duration is constant so that a temporal ratio process could provide the basis for numerical discrimination. Broadbent et al (1993) have demonstrated that a reference memory representation of number can be derived from two separate vectors representing interevent duration and total duration. However, a formal means of extracting this numerical information from reference memory has yet to be developed.

The distinction between an event mode and a temporal ratio process as the means of enumeration in the connectionist model has important implications for the debate over the nature of numerical competence in animals. An event mode, as shown in Section 1.2.2, meets the major criteria for counting defined by Gelman and Gallistel (1978). However, although a temporal ratio process can accurately represent the numerosity of an entire sequence of events, as required by the cardinal principle, there is no tagging of the discrete events which comprise the signal, and the criteria set by the one-one principle or the stable order principle are not met. In the case of a temporal ratio process, then, numerical discrimination cannot be described as counting because it does not meet the criteria set by the formal definition of counting. This important issue is addressed more fully in Chapter 2.

1.3.2 The behavioural theory of timing.

The behavioural theory of timing (BeT, Killeen & Fetterman, 1988) is an alternative to cognitive models of animals timing such as the connectionist and the mode-control models (Broadbent, Church, Meck and Rakitin, 1993; Church & Broadbent, 1990; Gibbon, 1997;

Gibbon & Church, 1984; 1990). BeT proposes that an internal Poisson pacemaker controls the transition through successive behavioural states, which are characterised by a unique class of adjunctive behaviours that may "come to serve as discriminative stimuli for subsequent responses" (Killeen & Fetterman, 1988, p. 274). Compared with the mode-control model, BeT model retains an internal pacemaker but behavioural states take the place of the accumulator and no other mnemonic or cognitive decision processes are invoked.

In BeT, each pulse from the pacemaker that is registered moves the animal from one behavioural state to the next and when the animal's behaviour results in reinforcement, this terminal behaviour becomes associated with the current behavioural state. The scalar property is accommodated by proposing that pacemaker rate is determined by rate of reinforcement which must vary inversely with the interval being timed. For example, if reinforcement is available after a fixed duration (T) in one condition, the number of pulses emitted by the pacemaker is $N = T\lambda_T$, where λ_T is the pacemaker rate associated with the reinforcement rate, $1/T$. N determines the current behavioural state (S_n) of the animal, which becomes progressively associated with the reinforced behaviour at T. If the interval to reinforcement is doubled in a second condition ($2T$), the reinforcement rate is halved and the adjusted pacemaker rate becomes,

$$\lambda_{2T} = \lambda_T/2, \tag{1.5a}$$

giving,

$$2T\lambda_{2T} = T\lambda_T = N, \tag{1.5b}$$

and thus the animal finds itself in the behavioural state S_n at $2T$ for the second condition compared to T for the first condition. This inverse relationship between reinforcement rate and pacemaker rate results in the scalar property because variability is proportional to the average length of the behavioural states, and response probability distributions around T and $2T$ superpose in relative time.

BeT has been applied to a several different timing procedures, giving a good account of the data and it is difficult to distinguish empirically from the information processing model of timing. However, Leak and Gibbon (1995) have argued that simultaneous timing provides a distinction between the two models. For the information processing model, pulses from the pacemaker are

gated into separate accumulators during simultaneous timing, so that the values in each can be transferred separately to reference memory. In this way, the timing proceeds in parallel beyond the pacemaker with each stream operating as if it were timing a separate interval and the scalar property is maintained. The BeT, however, must rely on separate behavioural states being associated with each target interval in the case of simultaneous timing. Pacemaker rate will be determined by the average rate of reinforcement and, because the average length of behavioural states are the same, timing should be just as precise at all target intervals, and response distributions would not superpose. Contrary to the BeT predictions, Leak and Gibbon (1995) found that the variance in the response distributions around target times obeyed the scalar property during simultaneous timing.

BeT does not deal explicitly with counting external events although counting (accumulation) at the pacemaker level is fundamental to BeT (c.f., Killeen, 1994). Numerical discriminations could be successfully accomplished if successive events drove the transition between behavioural states. However, this explanation may have difficulty in accounting for simultaneous timing and counting, particularly where post-sequence cues indicate whether numerical or temporal information should guide response choice (Roberts & Mitchell, 1994). Another concern is the plausibility of BeT when timing in the milliseconds range where pigeons can accurately discriminate between durations shorter than inter-response intervals (i.e., < .25 s) and it is questionable whether any reliable, discriminable transitions between other overt[4] behaviours can occur on this time scale.

1.4 Analysis of Variability in Timing and Counting.

The role of the cerebellum in timing is of major interest to the current study and a subsequent section (1.6) will review the existing evidence and theoretical viewpoints. One important hypothesis is that the cerebellum operates as an independent timing mechanism in the

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[4] If one is appealing to internal behaviours, such as internal physiological states, one may as well go all the way and appeal to brain states.

milliseconds range (Ivry, 1996; Ivry & Keele, 1989). However, the generalised Weber function described in Section 1.1.3 can accommodate changes in sensitivity to timing, which might otherwise suggest the existence of an independent millisecond timer, and offers tentative evidence that a single extended timing system may be responsible for temporal discrimination in the millisecond and seconds range. The purpose of the formal analysis presented here is to show how different sources of variance that have been identified as important to seconds range timing (e.g., Gibbon, Church & Meck, 1984) influence temporal discrimination in the milliseconds range. The impact of these sources of variance on milliseconds timing suggests an alternative hypothesis for cerebellar involvement in timing within the framework of the mode-control model. Furthermore, the analysis of variance in counting provides the rationale for testing this alternative hypothesis through the cerebellum's influence on numerical discrimination.

The scalar property and the resultant superposition of response distributions places strong constraints on the types of variance and decision rules that are admissible in modelling temporal discrimination. On this basis, Gibbon and his colleagues (e.g., Gibbon, 1991, Gibbon & Church, 1984; Gibbon et al, 1984) have provided several detailed analyses that determine the decision rules and sources of variance in the mode-control model which can account for superposition and the shape of experimental response distributions. The nature of the comparator process at the decision stage of the model is central to these analyses and is treated first (Section 1.4.1). Section 1.4.2 describes the analysis of sources of variability in timing (reviewed in Gibbon, 1991). I then develop a similar analysis for counting in Section 1.4.3.

Following the convention adopted by Gibbon et al (1984), random variables are designated by lowercase letters and their expected or mean values by the corresponding uppercase letter (e.g., $E[t^*] = T^*$). An asterisk designates parameters drawn from reference memory distributions (i.e., T^* represents the target duration) with the exception of k^* which represents memory storage speed. A summary of all parameters that are used in Section 1.4 and their relationship to the mode-control model is provided by Table 1.1.

1.4.1 The decision rule.

In determining appropriate rules for the comparator process, two types of decision rule have been examined under the assumption of no-variance timing. One type of rule is based on relative differences between current accumulator values and a sample drawn from the reference memory distribution, a relative discrepancy rule. An example of a relative discrepancy rule, the relative proximity rule, requires a response whenever,

$$|(M^* - M)/M^*| < 1 - B, \tag{1.6}$$

where M^* is the reference memory value of the reinforced duration or number, M is the current accumulator value and B is a response criterion (Gibbon, 1991). By contrast, the second type of rule is simply based on absolute discrepancy and requires a response whenever,

$$|M^* - M| < 1\text{-}B. \tag{1.7}$$

These rules can be applied to temporal generalization, the break point in FI timing or the break point and giving up time in the peak procedure. The important result is that a comparison of the relative and absolute discrepancy rules shows that only the relative discrepancy rule can accommodate superposition (Figure 1.6A, see also Gibbon et al, 1984). Even when several sources of variance are added, the absolute discrepancy rule is inconsistent with the scalar property.

Relative discrepancy rules have been developed or elaborated for specific timing procedures but all converge on a similar quantitative form. For example, in the psychophysical choice procedure a rule known as "Sample Known Exactly" may be the appropriate form (Gibbon, 1981,1991). This similarity rule requires a long response whenever,

$$(M_L^*/M\ )/(M/M_S^*) < B, \tag{1.8a}$$

where M_L^* and M_S^* are samples from the reference memory distributions for the long and short durations, respectively, and M is the current accumulator value. For numerical discrimination the similarity rule requires a many response whenever,

$$(M_M^*/M\ )/(M/M_F^*) < B, \tag{1.8b}$$

where M_M^* and M_F^* are samples from the reference memory distributions for many and few events, respectively.

Table 1.1

Summary of characters used to represent random variables and variance in the formal analysis of timing and counting in Section 1.4.

Variable [variance]	Description
T, t	Real time.
N, n	Number of events.
Clock stage	
Λ ,λ	Lamda, the pacemaker rate which is assumed constant within trials. The mean value is the mean rate across trials.
τ^*, τ	The effective duration during which pulses accumulate.
T_2,t_2, $[\sigma_2^2]$	Latency to open the switch.
T_0, t_0, $[\sigma_2^2]$	The difference between switch closure and re-opening and, thus, the threshold for timing.
M_r, m_r, $[\sigma_r^2]$	Residual value after the accumulator is cleared or reset.
Memory/decision stages	
M_S^*, M_L^*, M_F^*, M_M^*, M_T, m_t, M_N, m_n, M_T^*, m_t^*, M_N^*, m_n^*	Magnitude in memory. Subscripts indicate the particular stimulus dimension that generated the reference memory value. For time, T, t = time, S = short, L = long. For number, N, n = number , F = few, M = many. Asterisks denote reference memory magnitudes.
K^*, k^*	Weighting representing the distortion of magnitudes transferred from the accumulator or working memory to reference memory; sometimes referred to as memory storage speed (Meck & Church, 1987).
B, b	The response criterion or threshold at the decision stage of the mode-control model.
S, s, $[\sigma_s^2]$	Scalar random variable that summarises the product of the memory storage variable (k^*)and the response criterion variable (b).
Summary models	
A, B, C	Summary variables used by Killeen & Weiss (1987) to represent scalar, Poisson, and constant sources of variance in timing, respectively.
a_0, a_1, a_2	Summary variables used by Gibbon (1991) to represent constant, Poisson, and scalar sources of variance in timing, respectively.

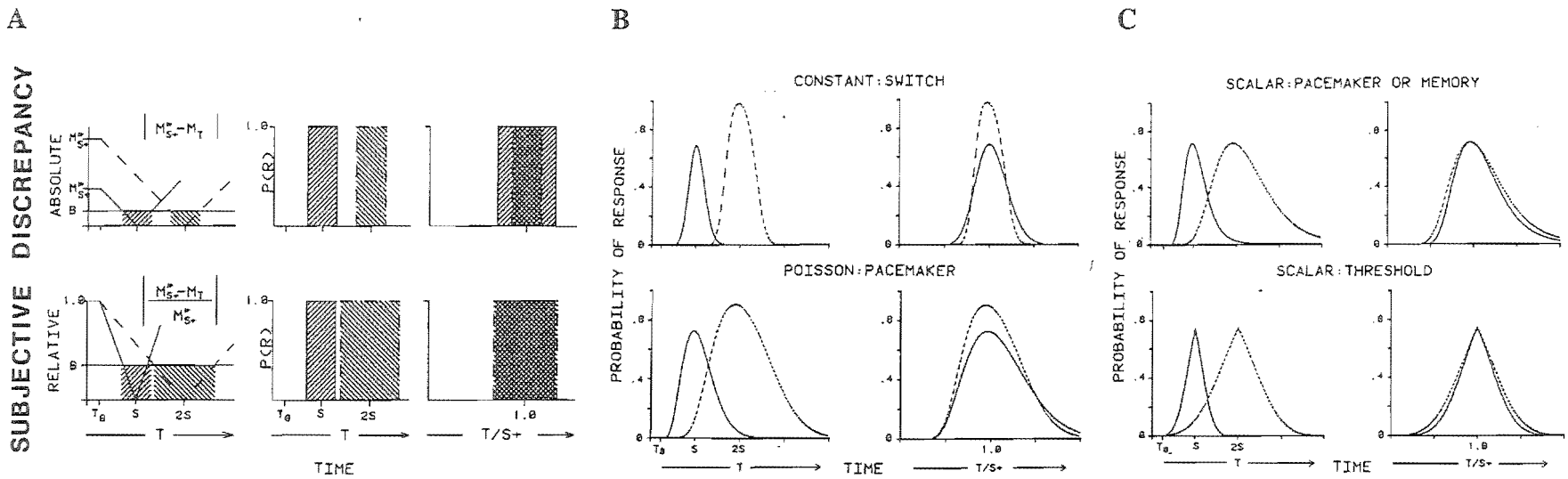

Figure 1.6. Panel A: Two possible decision rules, the absolute discrepancy rule (top row) and the relative discrepancy rule (bottom row). The left column shows the subjective difference between the accumulator value and the reference memory value as a function of signal duration with two different target durations (S+). The right two columns show response probability as a function of real time (middle column) and of relative time (right column). Panel B: The response probability gradients as a function of real time (left column) and relative time (right column) with the switch as the only source of variance (top row) or with Poisson variance in the pacemaker as the only source of variance (bottom). Panel C: The response probability gradients with the memory variance only (top row) or threshold (comparator) variance as the only source of variance (bottom) in real time (left column) and relative time (right column). Reproduced from Gibbon et al (1984), see text for details.

Multiplying both sides of Equation 1.8 by M gives,

$$M > G/B^{0.5}, \tag{1.9}$$

where $G = (M_S\, M_L)^{0.5}$ or $(M_F\, M_M)^{0.5}$ is the geometric mean of the extremes (Allan & Gibbon, 1991). Multiplying Equation 1.6 by M^* gives a similar result,

$$M > BM^*, \tag{1.10}$$

although the interpretation of B may differ between the contexts in which the rules apply (Gibbon, 1991). There are no subscripts to M and M* in Equations 1.6, 1.7, 1.9 and 1.10 because these terms refer to memory magnitudes that can be related to either timing or counting.

1.4.2 Sources of variability in timing.

Gibbon's (1990) analysis of variance in the breakpoint for fixed interval timing provides a relatively straight-forward example of a componential analysis of variance in timing. In Figure 1.7, the magnitude in the accumulator is shown to be current time, t, less the difference in switch latency ($_o = t_1 - t_2$; the threshold of timing), multiplied by pacemaker rate, $m_t = \lambda(t - t_0)$. On a certain proportion of trials when reinforcement is delivered the accumulator value is transformed by memory storage speed, k^*, and passed into reference memory so that $m^* = k^* m_t^*$ (not shown in Figure 1.7). Substituting these values for M and M^* in Equation 1.10 gives,

$$\lambda(t - t_0) = bk^* m_t^* t \tag{1.11a}$$

where $m_t^* = \lambda^*(t^* - t_0^*)$.

Simplifying and assuming a constant pacemaker rate,[5] $\lambda^* = \lambda$, the break point occurs at,

$$t_b = bk^*(T^* - t_0^*) + t_0. \tag{1.11b}$$

The variance attributable to the individual random variables in this function that are associated with pacemaker, switch, memory or comparator can be explored by setting the value of all

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[5] This assumption is convenient because a variable pacemaker introduces a scalar source of variance that is indistinguishable from other sources of scalar variance (Gibbon, 1991).

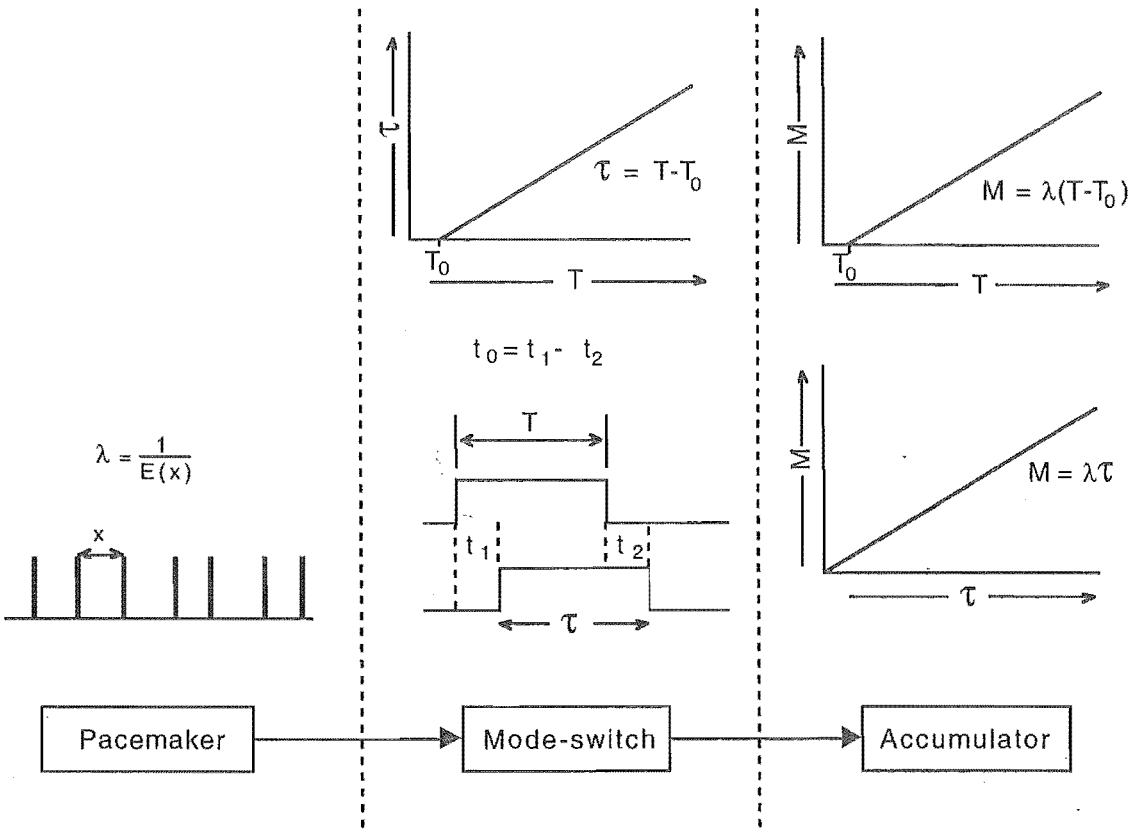

Figure 1.7. Clock processes during timing (the run mode), adapted from Gibbon (1991). See text and Table 1.1 for details.

remaining variables constant at their mean values (Gibbon et al, 1984). A model for overall variance in timing can then be derived by combining the individual variance of all random variables according to the variance sum and variance product laws[6]. The following analysis describes variance attributable to the pacemaker, switch mechanism, and memory and comparator processes. In the description below, recall that variables set at their mean values are in upper case.

1. Pacemaker variance: There are two sources of variance at the pacemaker stage. First, assuming that variation in interpulse interval is a Poisson process,

[6] The variance sum law states that the variance of the sum or difference between two random variables, a & b, is $\sigma^2_{a\pm b} = \sigma_a^2 + \sigma_b^2 \pm 2\rho\sigma_a\sigma_b$. The variance product law states that the variance of the product of two random variables is $\sigma^2_{ab} = \sigma_a^2\sigma_b^2 + \sigma_a^2 b^2 + \sigma_b^2 a^2$. The reader is also reminded that multiplying a random variable by a

then the time to reach a fixed number of pulses, say the criterion number of pulses, τ^*, becomes a gamma variate with a mean equal to the product of the criterion and the mean interpulse interval, $1/\lambda$,

$$E(t) = \tau^*, \tag{1.12a}$$

and

$$Var(t) = \tau^*/\lambda^2, \tag{1.12b}$$

where $\tau^* = T^* - T_0^*$ (Gibbon, 1990).

It is clear from this equation that variance from a Poisson pacemaker is directly proportional to the reinforced time, $T^* - T_0^*$. If this is the only source of variance during timing then, as pointed out by Gibbon et al (1984), variability does not rise rapidly enough with increases in reinforced time to accommodate superposition (Figure 1.6B, top panels, p. 29) which at least requires that variance is proportional to the square of the mean. Thus, Poisson pacemaker variance cannot operate as the sole source of variability in interval timing.

Second, in Equation 1.11 a constant pacemaker rate is assumed but if the pacemaker rate varies normally from trial to trial around a mean, Λ, scalar variation is introduced at the clock stage. As the only source of variability, a drifting pacemaker rate, in combination with the relative discrepancy rule, gives a close approximation of superposition but is indistinguishable from other sources of scalar variance in the memory and decision stages of the model (Gibbon et al, 1984).

2. Mode-switch variance. Several sources of variability are related to the switch mechanism during timing. The variability between the latency to close (t_1) and reopen (t_2) the switch introduces a constant variability to the threshold for timing ($t_0 = t_1 - t_2$). The switch closure latency, t_1, may also reflect variability in

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constant multiplies the standard deviation by the constant and the variance by the square of the constant.

resetting the accumulator before timing of each new trial begins (e.g., Cabeza de Vaca, Brown, & Hemmes, 1994). Any residual accumulation that remains from a previous trial effectively reduces t_1 and may lead to a negative t_0. Although different interpretations of switch latency, t_0, are possible, the important feature of this variable is that it represents any variance that is introduced at the onset and offset of timing. Setting non-switch variables constant at their mean values gives,

$$t_b = BK^*T^* + t_0 - BK^*t_0^*, \tag{1.13a}$$

and thus,

$$\mathrm{Var}(t_b) = \sigma_0^2[1 + (BK^*)^2], \tag{1.13b}$$

where $\sigma_0^2 = \mathrm{Var}(t_0)$.

For timing then, switch variance is a constant source of variability because $\mathrm{Var}(t_b)$ is independent of time and does not influence variance around the breakpoint, t_b. Switch variance is untenable as a sole source of variability in timing because the spread in response probability distributions remains the same irrespective of reinforced time (Figure 1.6B, bottom panels, p. 29, see also Gibbon et al, 1984).

3. Memory and comparator variance: Equation 1.8 shows that in determining the break point, reinforced time is transformed multiplicatively by the response criterion threshold, b, and memory storage speed, k^*. To simplify matters, these variables can be summarised by a product random variable, $s = bk^*$, so that setting all other random variables constant at their mean values, the breakpoint is given by

$$t_b = s(T^* - T_0) + T_0, \tag{1.14a}$$

and thus,

$$\mathrm{Var}(t_b) = \sigma_s^2 T^{*2} - \sigma_s^2 T_0^2, \tag{1.14b}$$

where $\mathrm{Var}(s) = \sigma_s^2$.

This function satisfies the scalar property because variance is proportional to the square of remembered time and response probability functions generated by

these equations will superpose in relative time. Gibbon et al (1984) conducted a more detailed analysis of memory and response criterion variance and found that both provided rough superposition when acting alone (Figure 1.6C, p. 29). The response distributions with response criterion variance as the sole source of variance were found to be qualitatively different from the experimental data (Figure 1.6C, bottom panels, p. 29), although the combination of response criterion and memory variance may provide a better model of the data than either form of variability alone.

On the basis of the preceding analysis, Gibbon (1990) has shown that the simultaneous contribution of pacemaker, switch, memory and comparator variance to overall variance at the breakpoint is given by,

$$E(t_b) = BK^*T^* + T_0(1 - BK^*), \tag{1.15a}$$

and

$$\mathrm{Var}(t_b) = \sigma_o^2(1 + B^2K^{*2} + \sigma_s^2) + (2BK^*/\lambda)(T^* - T_0) + \sigma_s^2(T^* - T_0)^2, \tag{1.15b}$$

or,

$$\mathrm{Var}(t_b) = a_0 + a_1(T^* - T_0) + a_2(T^* - T_0)^2, \tag{1.15c}$$

where a_0, a_1 and a_2 summarise the constant, Poisson and scalar sources of variance. The standard deviation, then, is asymptotically linear in remembered time and for reasonable choices

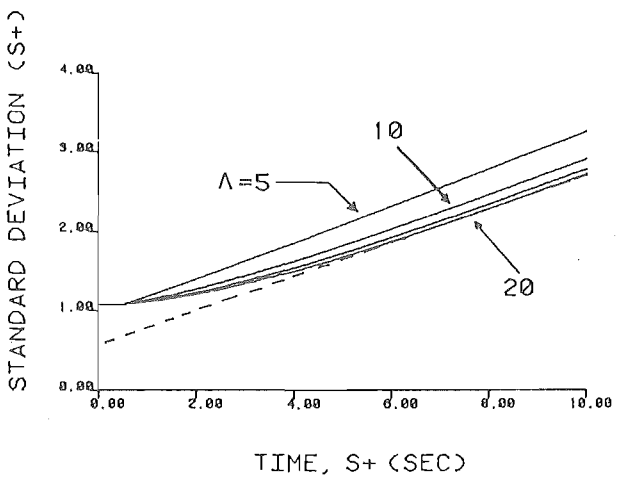

Figure 1.8. Standard deviation as a function of time with various pacemaker rates from 5 to 50 (reproduced from Gibbon et al, 1984).

of parameter values "scalar sources dominate variance in the seconds to minutes ranges ..." (Gibbon et al, 1984,p. 62, Figure 1.8).

Although developed primarily on the basis of data from seconds range timing, this model (Equation 1.15b and c) can also account for timing performance in the milliseconds range. Equation 1.15c is identical in form to a model derived from fundamentally different assumptions by Killeen and Weiss (1987, their Equation 9),

$$\sigma^2 = \underline{A}t^2 + \underline{B}t + \underline{C}. \tag{1.16}$$

Setting $a_1 = 0$ and $\underline{B} = 0$ in Equations 1.15c and 1.16, respectively, both converge on Getty's (1975) generalised Weber's law (Equation 1.2, $\mathrm{Var}(t) = (kt)^2 + c$) which provides a good description of variance in timing below 1 s for both humans and animals (Church Getty and Lerner, 1976; Fetterman & Killeen, 1992; Getty, 1975).

1.4.3 Sources of variability in counting.

In this section I have adapted Gibbon's (1990) analysis of variance in timing and extended it to counting, based on the event mode at the clock stage of the mode-control model of timing and counting. For the purpose of comparison with the analysis of timing I consider the case where reinforcement becomes available after a fixed number of events and the break point is given by n_b. Figure 1.9 shows the details of the clock stage during counting. The magnitude in the accumulator after n events is $M_N = \lambda n t_2 + m_r$ and in reference memory, $M_N^* = \lambda^* K^* n t_2^* + m_r$, where m_r is the residual number of pulses left in the accumulator after it has been reset. Substituting these equations for M and M^* in Equation 1.10 gives,

$$\lambda n t_2 + m_r = bk^* (\lambda^* n t_2^* + m_r). \tag{1.17a}$$

Simplifying and assuming a constant pacemaker rate, $\lambda^* = \lambda$, as before, the break point occurs at,

$$n_b = bk^* n(t_2^*/t_2) + m_r(bk^* - 1), \tag{1.17b}$$

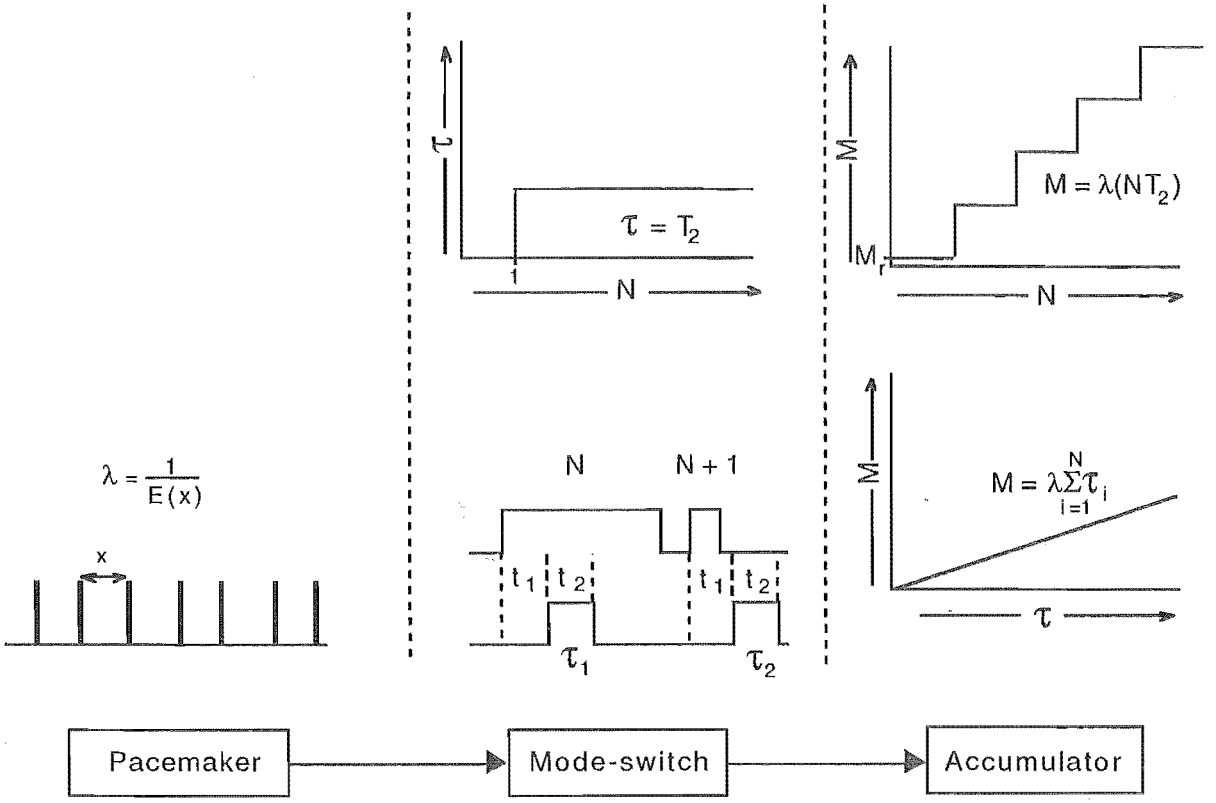

Figure 1.9. Clock processes during counting (event mode). See text and Table 1.1 for details.

number of events. Switch latency has become a ratio random variable that enters into the system twice, once at reinforcement and once for the current accumulator value and is now proportional to the number of events. As with the analysis of timing, the following analysis describes variance attributable to the pacemaker, switch mechanism and memory and comparator processes.

1. Pacemaker variance: Following the analysis of pacemaker variance for timing, the mean time, τ^*, to reach the average number of pulses accumulated for each count, λT_2, is a gamma variate with mean and variance given by Equation 1.12 where the mean break number, n_b, is the nth sum of these gamma variates given by,

$$n_b = N\ \tau^*, \tag{1.18a}$$

with

$$\mathrm{Var}(n_b) = N^2\tau^*/\lambda^2 \qquad (1.18b)$$

so that it is immediately clear that during counting, in contrast to timing, pacemaker standard deviation is proportional to the number of events.

2. Mode -switch variance. The only source of variability related to switch processes during counting comes from variance in t_2. The switch closure latency, t_1, does not enter into the system if t_1 and t_2 are assumed to be independent and t_1 is shorter than the interevent interval. Reset variance , m_r, is a constant source of variance that becomes distinguishable from switch variance in counting. If the only source of variance during counting is in switch latency, the break point is given by,

$$n_b = NBK^*(t_2^*/t_2) \qquad (1.19a)$$

and so

$$\mathrm{Var}(n_b) = (NBK^*)^2\sigma_t^2 \qquad (1.19b)$$

where $\sigma_t^2 = \mathrm{Var}(t_2^*/t_2)$ and once more, in contrast to timing, switch latency variance is proportional to the stimulus dimension, number.

3. Memory and comparator variance. As with timing, memory and comparator variability can be summarised by a single random variable, $s = bk^*$. Setting all other variance constant at its mean values the break point is given by,

$$n_b = Ns \qquad (1.20a)$$

and then

$$\mathrm{Var}(n_b) = N^2\sigma_s^2 \qquad (1.20b)$$

where σ_s^2 is the variance of the product random variable s and, as with timing, displays the scalar property.

When the variance from pacemaker, switch and memory and comparator processes operate simultaneously, the expected value of the break point is given by,

$$E(n_b) = BK^*N + M_r(BK^* - 1), \tag{1.21a}$$

and thus

$$\mathrm{Var}(n_b) = (\sigma_s^2\sigma_r^2 + M_r^2\sigma_s^2 + \sigma_r^2[B^2K^{*2} - 1]) + N^2(\sigma_s^2\sigma_2^2 + \sigma_2^2 B^2K^{*2} + \sigma_s^2), \tag{1.21b}$$

where σ_s^2 and σ_2^2, respectively, summarise memory and comparator variance and switch latency variance as before, and $\sigma_r^2 = \mathrm{Var}(m_r)$, or stated more simply,

$$\mathrm{Var}(n_b) = c_0 + c_2N^2 \tag{1.22}$$

where c_0 and c_2 summarise the constant and scalar sources of variance in counting. This equation is similar to the summary equation for variance during timing (Equation 1.15) with $a_1 = 0$, except that c_0 and c_2 summarise different sources of variance than a_0 and a_2. Most importantly, switch variance (or any variance introduced by operation of the switch) is constant in timing and does not contribute to scalar variance whereas switch variance makes a substantial contribution to scalar variance in counting.

1.4.4 Simultaneous sources of variability in counting and timing: An exploration.

In this section I compare the influence of switch variance with that of memory and comparator variance on overall variability in models of variance for counting and timing. The model for timing is based on Gibbon's (1990) analysis of variability in timing (Equation 1.15b). The model for counting is based on that developed in the current thesis as an extension of Gibbon's work on timing (Equation 1.21b). The parameter values used in the simulations are summarised in Table 1.2. It is important to note, however, that it is the qualitative nature of the simulations rather than the quantitative aspects which are of interest to the arguments developed here. The simulations are provided as part of the exploration of possible roles for the cerebellum in timing and counting processes.

Table 1.2
Parameter values for the simulations depicted in Figure 1.9 and 1.10

Parameter	Control value	Switch	Memory/comparator
λ	50	-	-
BK^*	1.1	-	-
σ_s	0.04	-	0.08
M_r	0.0	-	-
σ_r	0.0	-	-
T_0	0.2	-	-
σ_0	0.04	0.08	-
σ_2	0.04	0.08	-

The simulations in Figure 1.10 clearly show that increased switch variance (grey line) has a far greater impact on overall variability in the millisecond range (left panel) compared with the seconds range (right panel). As suggested by Gibbon et al (1978), constant variance appears to be masked by scalar variance at longer durations. By contrast, an increase in memory/comparator variance proportionately increases total variability in timing over all but the very shortest durations. Depending on the values given to the underlying parameters, and in contrast to seconds range timing, constant sources of variance may override scalar sources of variance when durations become very short.

The impact of increased switch variance on overall variability in counting is quite different to its impact on seconds range timing (Figure 1.11, grey lines). In counting, an increase in switch variance has a similar effect to an increase in memory/comparator variance to produce an increase in overall variability that is proportional to number. Increased memory/comparator variance produces linear changes in overall variance in counting that are similar to those found in seconds range timing.

On the basis of these simulations, then, experimental manipulations that disrupt switch processes should impair performance in counting and in milliseconds timing but should leave seconds range timing relatively unaffected. By comparison, experimental manipulations that disrupt memory/comparator processes should disrupt both counting and seconds range timing performance. Disruption of memory/comparator processes should also produce deficits in millisecond range timing that are similar to those found in seconds range timing. However, for extremely short intervals, and depending on the level of constant variance, subtle disruption of

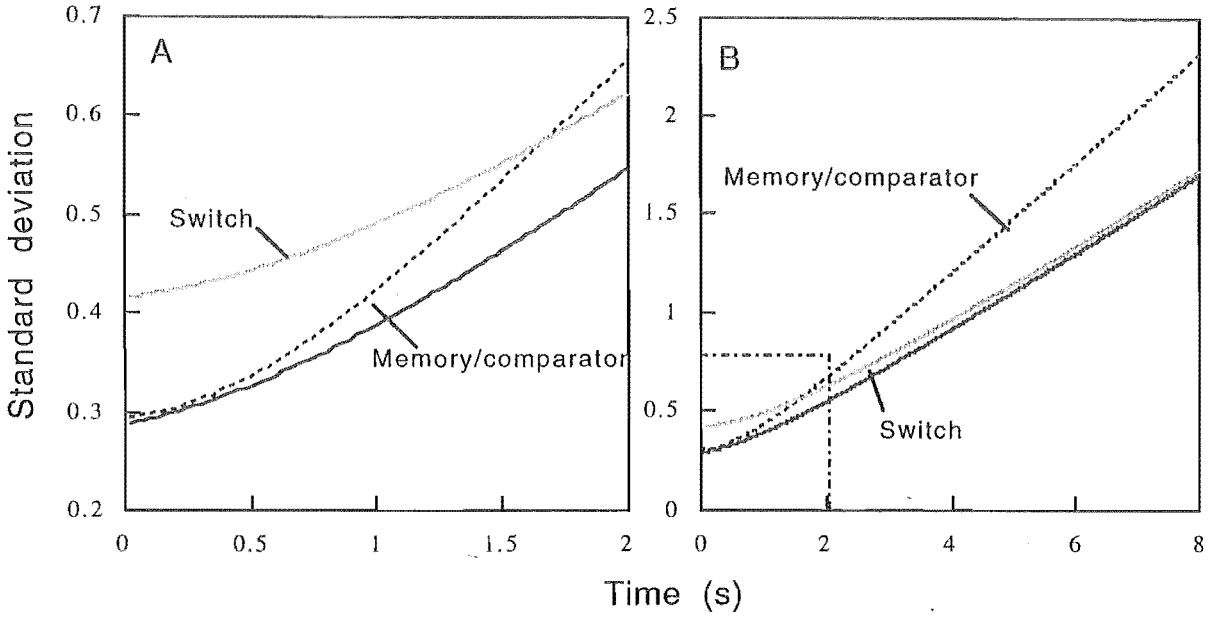

Figure 1.10. Standard deviation as a function of time: A comparison of the effects of increased switch variance (grey line) and memory comparator variance (dashed line) with control values (solid line). The left panel is the expanded inset from the right panel.

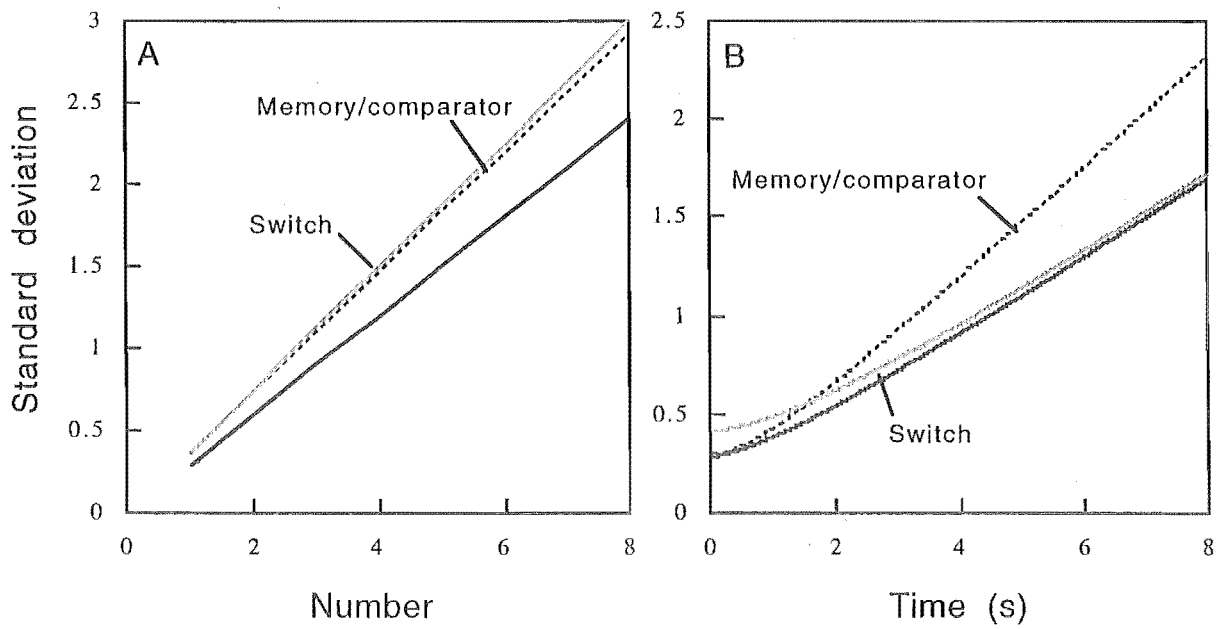

Figure 1.11. Panel A: Standard deviation as a function of number (left panel) and time (right panel) comparing of the effects of increased switch variance (grey line) and memory comparator variance (dashed line) with control values (solid line).

memory/comparator processes may not manifest themselves because they are masked by constant variance.

These same conclusions can be given greater generality, for timing, within the framework of the generalised Weber model (Equation 1.2). In this context, a change in *any* source of constant variance for timing will have a relatively greater impact on milliseconds range timing and will tend to be masked by scalar sources of variance in the seconds range (Figure 1.10). In addition to variance generated by noise in central switch processes, attentional deficits, other noise in perceptual systems outside the central timing mechanism or increased variance in the accumulator reset residual (i.e., σ_r^2) all contribute to constant variance and have a relatively greater impact on milliseconds range timing than seconds range timing. In timing, variance from attentional, perceptual or accumulator reset processes are all combined in switch closure variance (t_1, Figure 1.7) and are indistinguishable from variance directly associated with switch operation (i.e., variance common to both t_1 and t_2). For example, increased variability in the latency to start timing (t_1) associated attentional processes adds constant noise to timing by increasing variability in t_0. In contrast, t_1 has little impact on counting as long as t_1 latency is shorter than the interevent interval (see Figure 1.9). Thus, deficits in millisecond range timing, but not in seconds range timing or counting, might result from increased constant variance from any source of constant variance in timing other than switch processes. However, disruption of central switch processes (i.e., both t_1 and t_2) should impact on timing and counting in such a manner as to impair millisecond timing and counting performance while sparing seconds range timing performance.

1.5 The Neurobiological Basis for the Mode-control Model.

Animal lesion work and neuropharmacological studies provide important evidence for the neurological basis of interval timing and its constituent processes. Hippocampal, frontal, cholinergic and dopaminergic systems all appear to be involved in seconds range timing (Gibbon et al, 1997; Meck, 1998a; Meck & Church, 1988). This section examines the evidence

suggesting dissociable, but related, roles for these brain structures and neurotransmitter systems in the clock and memory/decision stages of the mode-control model (Church, 1984). Research with humans is also briefly reviewed (see Nichelli, 1995, for a more extensive review).

1.5.1 The clock stage.

Several psychopharmacological studies have shown that the neurotransmitter DA modulates clock processes of the mode-control model (Meck, 1983, 1986; Meck & Church, 1987). Recent animal lesion work confirms these findings and suggests that the locus of dopaminergic influence on timing appears to be the nigrostriatal DA systems (Meck, 1997a), a finding that is also consistent with evidence that parkinsonian patients show deficits in interval and motor timing (Pastor & Artieda, 1996; Boyle, Freeman & Cody, 1996).

Studies with animals have shown that dopaminergic agonists and antagonists such as methamphetamine and haloperidol produce phasic shifts in time estimation whereas cholinergic drugs produce chronic shifts in remembered time (see Section 1.6.2 below). For example, in the peak or bisection procedures methamphetamine produces an immediate leftward shift of the peak time or PSE, respectively. These measures of subjective time slowly return to pre-drug levels (baseline) with continued training under drug treatment. When the drug treatment is withdrawn, an immediate rightward shift in peak time or PSE occurs, followed, once more, by a gradual return to baseline levels with subsequent training. These phasic shifts in subjective time are consistent with the notion that pacemaker rate is strongly correlated with levels of brain DA. If pacemaker rate is abruptly increased, the accumulator values reach the criterion for responding (a relatively fixed proportion of the reference memory value, Equation 1.7) more rapidly in real time and as a consequence, subjective time is shortened. However, reference memory values are gradually adjusted to reflect larger accumulator values that are now associated with the reinforced time(s), if the increased pacemaker rate is maintained, and temporal estimates return to baseline. When pacemaker rate decreases, as is the case when DA antagonists are administered or chronic DA agonists are withdrawn, the process is reversed (Meck, 1983; Meck & Church, 1987).

Methamphetamine does not appear to influence sensitivity to time, although acute administration of haloperidol increases the Weber fraction (Maricq & Church, 1983) whereas no change in Weber fraction is apparent after chronic treatment (Meck, 1983). There is also some evidence that the frontal cortex (FC) and nucleus basalis magnocellularis (NMB) may regulate this type of dopaminergic influence on pacemaker rate (Meck, 1997b).

Although neuroleptics such as haloperidol bind to various dopamine receptor sub-types and other neurotransmitter sites, dopamine D_2 receptors appear to be particularly important to pacemaker rate. For example, the efficacy of neuroleptics in shifting the PSE during a bisection task is strongly correlated to dopamine D_2 receptor affinity and shows no significant correlation with affinity to alpha noradrenergic (NE-α) and serotonergic (5-HT_1 & 5-HT_2) receptor sites (Meck, 1986).

Further evidence suggests that the basal ganglia provide the locus of dopaminergic influence on timing. Rats with lesions to the substantia nigra (SN) or the caudate putamen (CPu) lost all ability for temporal discrimination in the peak procedure (Meck, 1996). Administration of the dopamine precursor l-Dopa restored timing ability in SN but not in CPu lesioned rats. However, although they could not discriminate stimulus duration, CPu lesioned rats appeared to be able to express differential response rates associated with the relative reward value of different stimuli. In contrast, lesions to the nucleus accumbens (NAC) appeared to abolish the ability to determine the relative reward value of stimuli but did not disrupt timing performance. Meck (1996, 1997a) has proposed that the SN controls pulse generation and the CPu is involved in the accumulation process, possibly gating or switching pacemaker output. The NAC appears to be involved in judging the relative reward value of the signal and does not appear to be critical to temporal discrimination.

In contrast, recent evidence from human drug studies implicates both the mesolimbic and mesostriatal dopaminergic systems in timing. Rammsayer (1997) suggests that the mesolimbic system is involved in seconds range timing whereas the mesostriatal system plays a role in milliseconds timing. The atypical neuroleptic remoxipride, which appears to act preferentially on mesolimbic and mesocortical D_2 receptors, increased variance in the seconds range (1 s) only, whereas the potent systemic DA blocker, haloperidol, increased variance for timing in both the

seconds and milliseconds range (50 ms; Rammsayer, 1993, 1997; Rammsayer & Gallhofer, 1995; see also Rammsayer & Vogel, 1992). In addition, several studies with humans have shown that patients with degenerative diseases of the basal ganglia show deficits in temporal estimation and production (see Nichelli, 1993, Gibbon et al, 1997 for reviews). For example, parkinsonian patients show increased variance in timing and tend to over-estimate time in the seconds range (Pastor & Artieda, 1996) although both under- and over-estimation of inter-response times have been reported during finger tapping (Boyle et al, 1996; Pastor, Jahanshahi, Artieda, & Obeso, 1992). Using the method developed by Wing and Kristofferson (1973), Boyle et al (1996) also partitioned overall variability into that attributable to central timing (clock variability) or to motor implementation (motor variability). Using this analysis, they found that increases in *both* central timing and motor variance contributed to the greater overall variance during finger tapping in parkinsonian patients compared to age matched controls.

The data from studies of timing by parkinsonian patients are difficult to interpret in terms of the analysis of dopaminergic influence on pacemaker rate in animals because testing and training with humans usually occurs in a single session. Even if parkinsonian patients are tested off medication, which may reduce pacemaker rate, both training and testing would occur at the same reduced rate. Factors such as disease duration and history of medication also complicate any interpretation of the data. Nonetheless, data from parkinsonian patients clearly implicate the basal ganglia in clock processes for humans, in the milliseconds for motor timing and in seconds range for temporal discrimination.

1.5.2 Memory and decision stages.

The mode-control model assumes that the value of information transferred from the accumulator to reference memory is not only a function of pacemaker rate but is also determined by memory storage speed (k* in the formal analysis, see Section 1.5). Although memory storage speed varies markedly between animals, resulting in either consistent underestimation or overestimation of time, estimates of memory storage speed are relatively constant within subjects

(Church, 1984). Cholinergic drugs or nutrients that affect cholinergic function appear to produce distortions in estimated time by influencing the transformation of accumulator values into reference memory (Meck, 1983; Meck & Church, 1987a, 1987b). Cholinergic drugs do not produce any immediate change in timing performance and estimates of subjective time change only after chronic treatment. The cholinergic agonist, physostigmine, increases memory storage speed in a dose dependent manner (Meck & Church, 1987a). When drug treatment starts there is no immediate change in time estimation but with continued training under the influence of the drug, there is a subjective shortening of time to some asymptotic level. When drug treatment is discontinued there is no immediate change but temporal estimates gradually return to the level that prevailed prior to drug administration. The pattern of effects is the same for cholinergic antagonists except that the direction of the shift in temporal estimates is reversed. These chronic changes in temporal estimation imply a distortion in the reference memory values that form the basis of response criteria as opposed to the phasic shifts seen with dopaminergic drugs that imply changes in pacemaker rate, to which reference memory values can be adjusted.

Lesion studies suggest that frontal and hippocampal systems play an important, complementary role in modulating temporal memory processes (Olton, Wenk, Church & Meck, 1988; Meck, Church, Wenk, & Olton, 1987; Olton, 1989; Meck, 1988). Rats with lesions to the FC or NBM showed deficits in temporal estimation, consistent with a decrease in memory storage speed (i.e., overestimation similar to that produced by cholinergic antagonists) whereas fimbria fornix (FF) or medial septal area (MSA) lesions resulted in chronic underestimation of time. The ability of rats to simultaneously time multiple durations was also disrupted by FC and NBM lesions but not by FF and MSA lesions. However, rats with FC and NBM lesions retained the ability to interrupt timing during "gaps" in a signal whereas rats with FF and MSA lesions appeared to begin timing anew after the gap (Meck, Church & Olton, 1984). The cholinergic antagonist, atropine, also disrupted the timing of an interrupted signal in a similar way to FF and MSA lesions whereas the dopaminergic antagonist, haloperidol did not disrupt the timing of intervals with gaps (Olton, Meck, & Church, 1987).

Overall, the evidence from psychopharmacological and lesion work suggests that acetylcholine (ACh) is important to both working and reference memory. The frontal system

appears to regulate reference memory and divided attention whereas the hippocampal system is involved in temporal processing that requires working memory.

1.6 The Cerebellum and Timing.

Although very few animal studies have examined timing behaviour in the milliseconds range, the psychobiological and psychophysical evidence reviewed so far is consistent with the notion of a single distributed neural system that is responsible for timing from milliseconds to minutes. An alternative view, however, is that separate neural systems are responsible for milliseconds and seconds range timing and that milliseconds range timing is the responsibility of a task-independent timing system based in the cerebellum (Ivry, 1997; Ivry, 1993; Ivry & Keele, 1989; Keele & Ivry, 1990). This proposal is supported by evidence that cerebellar patients were impaired in both motor timing and the discrimination of brief durations (Ivry & Keele, 1989). To date, only one other published study and a preliminary report has examined the performance of cerebellar patients in interval timing (Nichelli et al, 1996; Malapani, Khati, Dubois & Gibbon, 1997, cited in Gibbon et al, 1997). It is also remarkable that there is little animal work on the neurobiological basis of temporal discrimination in the milliseconds range. This section begins with a brief description of cerebellar anatomy as a background to a review of the evidence for cerebellar involvement in human and animal timing and to the lesion experiments conducted in the current research.

1.6.1 Anatomy.

The gross morphology of the rat cerebellum can be described in terms of longitudinal and transverse subdivisions that conform to a general mammalian pattern. Two shallow rostrocaudal indentations on the dorsal surface of the cerebellum demarcate the vermis, a central longitudinal structure, from the lateral portions which constitute the cerebellar hemispheres, although recent

evidence suggests that the cerebellum can be divided into additional longitudinal compartments (e.g., two or more lateromedial zones, Ito, 1984). Superimposed upon these longitudinal subdivisions are a series of transverse sections, or lobules, that are defined by major fissures. The corpus cerebelli, which is separated from the flocculonodular lobe by the posterolateral fissure, is divided into anterior and posterior lobes by the primary fissure. In addition, the posterior lobe is subdivided, rostrocaudally, into the simplex lobule, crus 1 and crus 2 of the ansiform lobule, the paramedian lobule and the copula pyramis, by the posterior superior fissure, the intercrural fissure, the ansoparamedian fissure and the prepyramidal fissures, in that order. This nomenclature is usually combined with that used by Larsell (1937) who identified ten lobules (I to X) in the vermis of the cerebellum.

Histologically, the cerebellar cortex can be divided into three layers - the molecular, the Purkinje cell and the granular layer - that has two major types of afferent projections, mossy fibres and climbing fibres, both of which also send collaterals to the cerebellar nuclei. Mossy fibre afferents are relayed through granular cells to the parallel fibres which pass through the dendritic trees of Purkinje cells in the molecular layer of the cerebellar cortex. Estimates of the number of cells contacted by a parallel fibre varies from 45 to 1,100, although parallel fibres may not synapse with every Purkinje cell aborization that they pass through (Ito, 1984). In contrast, climbing fibres contact Purkinje cells on a one to one basis, although they also send collaterals to the cerebellar nuclei. The axons of the Purkinje cell provide the sole output of the cerebellum through the cerebellar nuclear complex and vestibular nuclei.

Afferents

Mossy fibre afferents project from the pontocerebellar and reticulocerebellar systems, and the spinocerebellar tract. The pontine and reticulotegmental nuclei provide a major projection into the cerebellar hemispheres and a far more restricted pattern of innervation in the vermis. Spinocerebellar projections provide a complementary picture. They terminate more heavily in the anterior lobe and copula pyramis, especially medially, and are entirely absent from the ansiform lobule. The pontine and reticulotegmental nuclei receive strong projections from sensorimotor, visual and auditory cortices and also receive inputs from other centers such as superior colliculus

and the lateral geniculate body. The inferior olive (IO) appears to be the only source of climbing fibres to the cerebellum although the IO receives inputs from many regions ranging from the lumbar spinal cord to the cerebral cortex (Flumerfelt & Hrycyshyn, 1984).

Efferents

The nuclear complex of the cerebellum can be divided into medial (fastigial), interposed (interpositus) and lateral (dentate) groups of nuclear cells. The vermis projects into the fastigial nucleus whereas the interpositus and dentate nuclei receive their input from the hemispheres, although dentate nucleus projections originate more laterally than those into the interpositus nucleus (Voogd, Gerritts, & Marani, 1985). The fastigial nucleus appears to project to multiple sites in the midbrain reticular formation, raphe nuclei, intermediate grey matter of the spinal cord and the ventro-lateral thalamus. It has also been proposed that in cats and monkeys forebrain structures such as septum, hippocampus and amygdala receive fastigial input. The dentate - interpositus nuclei send major projections to the red nucleus and ventrolateral thalamus but also supply input to the superior colliculus and periaqueductal grey. There is also evidence that the dentate and interpositus nuclei project to the SN. Degenerating terminals were found in the contralateral substantial nigra following unilateral lesions to the dentate and interpositus nuclei in the rat (Snider, Maiti, & Snider, 1976). A recent anterograde tracing study has shown cerebellar nuclei and basal ganglia projections to the thalamus are primarily segregated although there is some modest convergence on the ventral medial nucleus and parafascicular nucleus (Denaiu, Kita, & Kitai, 1996).

Electrical stimulation to the cerebellar nuclei in cats has provided some evidence of a direct functional interaction between the cerebellum and the basal ganglia (Nieoullon, Cheramy, & Glowinski, 1978). Stimulation of the fastigial nucleus increased DA release in the ipsilateral caudate nucleus, associated with decreased release in the corresponding SN; activity in the contralateral DA system was not affected. In contrast, unilateral stimulation of the dentate nucleus produced a decrease in DA levels in the ipsilateral caudate nucleus accompanied by an increase in the contralateral caudate nucleus. Opposite fluctuations were associated with these changes in the corresponding SN. These results, the evidence of convergent cerebellar and basal

ganglia projections in the thalamus and of more direct connections to the SN provide a possible basis for the cerebellar modulation of basal ganglia function (Denaiu et al, 1996; Denaiu & Chevalier, 1985), which may include interval timing processes (Meck, 1996).

An exception in humans to the general mammalian pattern is the greatly enlarged dentate nucleus in which a newly evolved part of the dentate nucleus, the neo-dentate, can be differentiated from the phylogenetically older part. The neo-dentate appears to project via the thalamus to prefrontal regions of the cerebral cortex providing a neuroanatomical basis for cerebellar involvement in cognitive and language functions in humans (Leiner, Leiner, & Dow, 1993).

1.6.2 Animal lesion work.

There appear to be only four animal studies that have examined the role of the cerebellum in timing (Clarke, Ivry, Grinband, Roberts, & Shimizu, 1996; Kirk, 1985; Perrett & Mauk, 1995; Perrett, Ruiz, & Mauk, 1993). These studies have examined cerebellar involvement in timing of the conditioned nictitating membrane response (NMR, Perrett & Mauk, 1995; Perrett & al, 1993) and on behaviour in a differential reinforcement of low rates of responding schedule (DRL) and in a fixed interval schedule (FI, Kirk, 1985). The conditioned NMR, DRL and FI involve the learned timing of behaviour although the temporal domains differ. The NMR appears to be limited to durations less than 1 s or 2 s whereas the DRL and FI schedules involve durations longer than a second. The preliminary work of Clarke et al (1996) appears to be the only study that has examined the effects of cerebellar lesions on the temporal discrimination in both the millisecond and seconds time ranges.

Kirk (1985) found that lesions of the fastigial nucleus and cerebellar vermis, but not lesions of the dentate nucleus, produced profound deficits in DRL acquisition after surgery. Response distributions of interresponse times (IRTs) for sham operated and dentate lesion rats had a similar peak and spread around the target duration (5 s). In contrast, the response distributions for the combined fastigial nucleus and vermis group (paleocerebellar group) showed a decrease

in peak time apparently as a consequence of an inability to suppress responding early in the delay interval. However, rats that received paleocerebellar lesions after preoperative DRL training showed performance that did not differ from the sham operated or dentate lesion groups. When paleocerebellum lesioned rats were trained on a FI 20 s schedule the median response time and the spread of response distributions did not differ from controls. On the basis of these results it was concluded that the DRL deficit following paleocerebellar lesions was the result of a tendency to perseverate in responding rather than a disruption of interval timing ability.

There is evidence that cerebellar lesions disrupt the timing of the conditioned NMR (Perrett & Mauk, 1995; Perrett & al, 1993). Perrett et al (1993) trained rabbits with standard Pavlovian conditioning procedures and delays between conditioned stimulus (CS) and unconditioned stimulus that ranged from 150 to 1000 ms. In rabbits that were trained with two different CSs of short and long durations (e.g, CS1 = 0.15 s, CS2 = 0.75 s), the latencies to onset and peak of the conditioned response were significantly shorter following lesions to the cerebellar hemispheres compared to preoperative latencies. In fact, for animals with large hemisphere lesions that included the anterior lobe, the response topographies for the two CSs were very similar to one another with the shortest post-lesion onset latencies at approximately 60 - 70 ms. In a subsequent study, Perrett & Mauk (1995) replicated these findings and provided additional evidence that the anterior lobe of the cerebellum was particularly important to accurately time NMRs. Rabbits with hemisphere lesions that did not include the anterior lobe continued to show appropriately timed conditioned responses whereas those with lesions that included the anterior lobe showed marked deficits in response timing. Taken together, the findings of Perrett and colleagues (Perrett & Mauk, 1995; Perrett & al, 1993) and Kirk (1985) suggest that the cerebellum is important to accurately timed behaviour in the milliseconds range but not in the seconds range.

Consistent with these findings is the pattern of deficits shown by rats with cerebellar lesions in a preliminary study of temporal discrimination in both the milliseconds and seconds range using the bisection procedure (Clarke et al, 1996). In the first experiment, rats were trained on alternative days to discriminate between either 0.3 s and 0.75 s or 25 s and 40 s, before being tested using standard psychophysical procedures. The animals then received either bilateral

electrolytic lesions of the dentate nucleus or sham lesions before being re-tested (Note: sham n = 3, cerebellar lesion n = 8). The Weber fractions cited in this thesis for Clarke et al's (1996) study were calculated from the PSEs and standard deviations they estimated from mean psychophysical functions. As might be expected given the generalised Weber's law, the Weber fractions for millisecond timing were higher than for seconds timing before surgery (Weber fractions = 0.24 and 0.17, respectively). Following surgery, the Weber fraction from the mean psychophysical function in the millisecond task increased more markedly for the cerebellar lesion group (Weber fraction = 0.28) compared with controls (Weber fraction = 0.25) whereas the Weber fractions were unchanged in both groups for the seconds range task. The only statistical tests that Clarke et al (1996) performed involved two summary measures of their own calculated on a trial by trial basis for each rat, a consistency score and a bias score. Their consistency score reflects any change in the acuity of timing relative to mean pre-surgery performance and appears to combine the traditional measures of p(A) and DL depicted in Figure 1.1. Their bias score reflects any postoperative change in the animals' tendency to respond on a particular lever (i.e., short or long) and as such combines position bias (p[Rl~A]) with response bias (PSE; see Section 1.1.1 and Data Analysis Experiment 2.1). Clarke et al found a significant increase in bias score towards the short lever in the lesion group. For the consistency score, there was a significant interaction due to a decrease in the consistency score for the milliseconds range compared with an increase for the seconds range. However, the decrease in consistency score was relatively transient and it returned to pre-surgery levels by about the fifth training session (2,500 trials). There were no significant changes for the 3 sham rats.

In Clarke et al's (1996) second experiment, naive rats were trained on a similar millisecond range discrimination (0.3 s to 0.8 s) and an intensity discrimination with brief duration (0.55 s) white noise stimuli prior to surgery (Clarke et al, 1996). Once more, millisecond timing performance was impaired following dentate lesions (sham n = 3, cerebellar lesion n = 9) with the Weber fraction increasing from 0.22 to 0.31 compared to 0.18 to 0.20 for sham operated rats; the PSE was the same across groups and pre- and post-surgery conditions so that the changes in Weber fraction reflect changes in standard deviation. The changes in Weber fraction for lesioned rats were also reflected in a significant decrease in consistency scores immediately

after surgery but in this second experiment there were no changes in the bias measure. Importantly, intensity discrimination was not disrupted by the lesions suggesting that millisecond timing deficits were not related to a general deficit in processing short duration stimuli. However, although histological analysis revealed that these lesions were larger than in the first experiment, these rats also showed good recovery of timing performance as measured by the consistency score.

The transient nature of the deficits shown by Clarke et al's (1996) cerebellar rats may be indicative of functional recovery within the cerebellum or, alternatively, they may indicate that the cerebellum plays a non-critical role in interval timing. Overall these results need to be treated cautiously for a two main reasons. First, the number of sham operated rats was small. Second, the summary measures consistency score and bias score confound independent aspects of psychophysical choice behaviour; overall performance (p[A]) with sensitivity (DL or Weber fraction) in the former, and position bias with response bias in the latter. However, provided these results can be replicated, they offer tentative evidence for some type of cerebellar involvement in milliseconds range timing for animals.

1.6.3 Timing by humans with cerebellar damage.

Temporal aspects of motor control and eyeblink conditioning have been shown to be disrupted in humans with cerebellar damage (Ivry, Keele & Diener, 1988; Topka, Valls-Sole, Massaquoi, & Hallett, 1993; Woodruff-Pak, Papka, & Ivry, 1996). Ivry et al (1988) examined the finger tapping performance of 7 patients that had been evaluated as having either lateral (n = 4) or medial (n = 3) cerebellar lesions. Separate estimates of variability attributable to a central time keeper and motor implementation, using Wing and Kristofferson's (1973) method, showed that patients with lateral cerebellar damage appeared to have deficits in central timing whereas patients with medial cerebellar damage appeared to have deficits in motor implementation. These findings suggest a dissociation of function between the medial and lateral

cerebellum in the control of repetitive movements with the cerebellar hemispheres playing a more important role in motor timing as opposed to implementation.

Humans with cerebellar damage also show deficits in classical conditioning whereas unconditioned responding is unimpaired. (Daum, Schugens, Ackermann, Lutzenberger, Dichgans & Birbaumer, 1993; Topka et al, 1993). For example, Daum et al (1993) found that only 2 out of 7 patients in their study showed any evidence for the acquisition of the conditioned response (CR) at all. Similar results have been reported by Topka et al (1993) who also found that cerebellar patients were severely impaired in the acquisition of the CR. The highest mean rate in any block of trials was less than 20% for cerebellar patients compared with 65% for controls. In addition, the timing of cerebellar patients' CRs tended to be inappropriately delayed (i.e., longer than the expected time of the unconditioned stimulus), a contrast to the rabbit study where CRs were inappropriately early (Perrett & Mauk, 1995; Perrett & al, 1993).

Recently, Woodruff-Pak et al (1996) found similar deficits in rate acquisition of the conditioned ipsilateral eye blink response in patients with unilateral cerebellar lesions compared with the contralesional eye and with controls (14% versus 60%, for ipsilesional and controls respectively). The ipsilesional CRs tended to be inappropriately delayed and cerebellar patients showed greater clock variability, but not motor variability, in the ipsilesional hand during repetitive finger tapping. Clock variability in finger tapping was also significantly correlated with percentage of CRs in control subjects, although a similar analysis was not done for cerebellar patients because of insufficient sample size.

Overall, studies with cerebellar patients support a role for the cerebellum in eyeblink classical conditioning which involves disrupted timing of the CR. On a cautionary note, however, the nature of CR timing deficit in humans with cerebellar damage is quite different to that found with rabbits (inappropriately late versus inappropriately early, for humans and rabbits respectively) and the classical conditioning deficits in cerebellar patients cannot be explained by impaired timing alone (Daum et al, 1993).

The timing deficits shown by cerebellar patients in classical conditioning and finger tapping provide support for the hypothesis that the cerebellum operates as a "specialised module for timing" (Ivry, 1997, p. 851; Ivry, 1993; Ivry & Keele, 1989; Keele & Ivry, 1990) in both the

perceptual and motor domains. Ivry and colleagues have argued that evidence from neurologically intact humans suggesting a relationship between variability motor timing and temporal discrimination in the millisecond range also supports this hypothesis (Ivry, 1996; Ivry & Hazeltine, 1995; Keele & Ivry, 1990; Keele, Pokorny, Corcos, & Ivry, 1985). Ivry and Hazeltine (1995) have shown that temporal variability in both motor and perceptual timing conforms to Webers law in the 325 to 550 ms range. In repetitive finger tapping, the Weber fraction (measured by the slope of variance as a function of duration squared, in this case) was lower compared to perceptual timing (a stair case method) although the authors suggest that the temporal demands for tasks may be quite different. When the motor timing task involved production of a single interval the Weber fractions were the same for motor and perceptual timing. This result is consistent with the earlier finding that variability in finger tapping and temporal estimation were correlated (Keele et al, 1985) which together suggest that motor and perceptual timing may have a common neural basis.

However, to date only two published studies have examined interval timing performance in patients with cerebellar damage (Ivry & Keele, 1989; Nichelli et al, 1996). Ivry and Keele (1989) compared performance in cerebellar, parkinsonian, cortical and peripheral neuropathy patients with elderly and college-aged controls on a temporal discrimination task and a motor timing task. The temporal discrimination procedure was a staircase method with comparison durations that were either shorter or longer than a standard fixed at 400 ms. For each subject, the standard deviation was estimated by adjusting the duration of the comparison intervals until they were correctly classified as either short or long with a probability of 90%. Only the cerebellar group showed significantly larger standard deviations when the performance of all patient groups was compared to elderly controls, although it should be noted that most parkinsonian patients were only tested while "on" medication. The results were similar for the motor timing task which involved a standard finger tapping procedure (12 to 14 paced finger taps followed by 31 unpaced finger taps). In this second task, cerebellar (and cortical) patients showed greater variability in inter-response times compared to elderly controls and parkinsonian patients among whom there were no differences. A further analysis of tapping variability revealed that the variability attributable to clock sources (and other non-motor sources) was

significantly higher for cerebellar patients whereas motor variability was similar to that of controls and parkinsonian patients.

On the basis of the findings that cerebellar patients were the only group to be impaired in both temporal discrimination and motor timing tasks, Ivry and Keele (1989) proposed that the cerebellum provides a critical component of internal timing processes whereas the basal ganglia are involved in determining non-temporal parameters associated with task performance (e.g., force control). The latter conclusion needs to be treated cautiously, however, because the timing performance of Ivry & Keele's Parkinson's disease (PD) patients is in contrast with the result of other studies where PD patients "off" medication showed deficits in both motor and perceptual timing (Boyle et al, 1996; Pastor et al, 1992). As stated earlier, there is also evidence that dopaminergic drugs influence interval timing performance in the millisecond range (Rammsayer, 1993, 1995; Rammsayer & Gallhofer, 1995; Rammsayer & Vogel, 1992). In particular, Boyle et al's (1996) detailed analysis of PD patients performance on finger tapping suggests that dopaminergic processes in the basal ganglia play an important role in precise motor timing and they concluded that "timing computations are not, as suggested by Ivry and his colleagues, the sole, or primary, preserve of the cerebellum (Keele & Ivry, 1987; Ivry et al, 1988; Ivry & Keele, 1989; Keele and Ivry, 1990)" (p. 67).

The second study to examine temporal discrimination in cerebellar patients used a standard bisection procedure across four time range conditions; 100 to 325 ms, 100 to 600 ms, 100 ms to 900 ms, and 8 s to 32 s (Nichelli et al, 1996). In the 100 to 325 ms condition there were no differences in performance between cerebellar and control subjects. In the 100 ms to 600 ms condition sensitivity to time was poorer for cerebellar patients (Weber fraction = 0.16) compared with control subjects (Weber fraction = 0.11) but otherwise performance in both groups was similar. For the 100 ms to 900 ms condition the PSE was shorter for cerebellar patients (PSE = 364 ms) compared with controls (PSE = 443 s) whereas the Weber fractions were similar. For the seconds range condition (8 s to 32 s), cerebellar patients showed a lower sensitivity to time compared with normal controls (Weber fraction = 0.24[7] and

[7] This reported value may be an error as the Weber fraction calculated from the mean PSE and DL comes to 0.34 whereas all other Weber fractions calculated from mean PSEs and DLs are the same as those reported.

Weber fraction = 0.14, respectively). However, the response distributions for cerebellar patients in the 8 s to 32 s condition were poorly fitted by the logistic function compared to controls (variance explained, 86% versus 96%, respectively) unlike the millisecond conditions where variance explained was similar between groups. This poor level of variance explained was significantly correlated with categories achieved and perseverative errors on the Wisconsin Card Sorting Test (WCST) for cerebellar patients. On this basis, the disrupted seconds range timing was interpreted by Nichelli et al (1996) as an impairment of sustained attention or strategy use.

While Nichelli et al's (1996) cerebellar patients had a problem with temporal discrimination in both the milliseconds and seconds range, the exact nature of these deficits is difficult to determine because of several methodological problems. The four time range conditions were not counter-balanced and all subjects appear to have been tested in the following order: 100 to 900 ms, 8 s to 32 s, 100 to 600 ms, and 100 to 325 ms. The different ratios of the short and long standard (i.e, 1:9, 1:4, 1:6, and 1:325, respectively for the conditions in order of presentation) may also have been problematic because Ferrara, Lejeune and Wearden (1997) have shown that sensitivity to time appears to increase with smaller ratios of training stimuli. In addition, concurrent vocalisation was used in the 8 s to 32 s condition to suppress chronometric counting but not in other conditions making it difficult to compare performance between seconds and milliseconds range timing. Given these methodological shortcomings, it is difficult to determine whether the higher Weber fraction for cerebellar patients in the seconds range condition was the consequence of a specific timing deficit or whether it was related to deficits in attentional difficulties found in cerebellar patients (Akshoomoff & Courchesne, 1992, 1994) or strategy use as indeed was suggested by Nichelli et al (1996) because of the poorer variance explained and its correlation with perseverative errors on the WCST. Furthermore, both these factors may have been compounded by possible interference from the concurrent suppression task. However, it should be noted that Gibbon et al (1997) report that deficits in seconds range timing were also found in cerebellar patients by Malapani, Khati, Dubois and Gibbon (1997, cited in Gibbon et al, 1997) although the details of this study were not given.

The results from the millisecond range conditions are also difficult to interpret because the cerebellar patient's performance was quite different in each of the 3 conditions tested. Nichelli et

al (1997) suggested that the lower PSE for cerebellar patients in the 100 to 900 ms condition may have been the result of a subjective shortening of the long standard relative to the short standard (i.e., the two standards were perceived as closer together), presumably because they felt this could be related to a common deficit associated with the higher Weber fraction in the 100 to 600 ms condition. They explained the failure to find deficits in the shortest time range condition (100 to 325 ms) by suggesting that these durations lie outside the range of cerebellar timing. However, another interpretation of the pattern of results in the 3 millisecond range conditions is possible. Cerebellar patients may have been slower to benefit from either practice across the millisecond conditions, the reduced ratio in the standards or a combination of both. Sensitivity to time was the same, and at its best, for both groups in the final condition (100 to 325 ms, cerebellars' Weber fraction = 0.10, controls' Weber fraction = 0.11). The control group had reached this level in the previous condition which was a improvement on performance in the initial condition (100 s to 900 ms, Weber fraction = 0.16, and 100 to 600 ms, Weber fraction = 0.11). By contrast, cerebellar patients maintained a similar level of sensitivity to time across these first two millisecond conditions (100 to 900 ms, Weber fraction = 0.15, and 100 to 600 ms, Weber fraction = 0.17).

Two recent imaging studies that examined brain activation during temporal discrimination and motor timing have implicated the cerebellum in millisecond timing (Jeuptner, Rijntjes, Weiller, Faiss, Timmann, Mueller, & Diener, 1995; Rao, Harrington, Haaland, Bobholz, Cox & Binder, 1997). The first study used positron emission tomography (PET) to examine changes in brain activity while subjects performed a temporal discrimination in which a short or long probe duration (0.2 s or 0.4 s) had to be judged as shorter or longer than an intermediate standard (0.3 s, Jeuptner et al, 1995). The second study used whole-brain functional magnetic resonance imaging (fMRI) to investigate changes in brain activity while subjects performed the standard unpaced finger tapping task (Rao et al, 1997). Both studies found increased activation of the cerebellum, thalamus and basal ganglia (putamen) during the experimental condition compared to a control task for the temporal estimation study and unpaced finger tapping for the motor timing study. The cingulate cortex appears to have been activated in the PET study only (temporal discrimination, Jeuptner et al, 1995) and the supplementary motor area (SMA) and inferior

frontal gyrus appear to have been activated in the fMRI study only (motor timing, Rao et al, 1997). Jeuptner et al (1995) concluded that the cerebellum was directly involved in timing without attempting to explain the increased activation of the putamen. Rao et al (1997) attributed a critical role in timing to the medial "pre-motor" loop consisting of SMA, the caudal putamen and ventrolateral thalamus, and ascribed a role of multisensory integrator to the cerebellum (c.f. Seitz, 1996).

In summary, the widespread anatomical connections of the cerebellum to other parts of the central nervous system provide a foundation for possible cerebellar involvement in cognitive functions. Some evidence suggests that millisecond timing is disrupted in rats following cerebellar lesions, although this deficit appears to be transitory, whereas seconds range timing appears to be unimpaired (Clarke et al, 1996). Humans with cerebellar lesions also show some deficits in interval timing for the millisecond range although this evidence is not yet convincing (Ivry & Keele, 1989; Nichelli et al, 1996). Seconds range timing may also be disrupted in cerebellar patients although it is possible that this deficit is not related to central timing processes (Nichelli et al, 1996). In addition, although imaging studies show that the cerebellum is activated during timing tasks, other brain regions such as the putamen and thalamus also become relatively more active. At present, the evidence for direct cerebellar involvement in temporal discrimination is tentative and the nature of the cerebellum's role in timing processes remains to be substantiated.

1.7 Aims of the Present Study.

The principal aim of the present study was to investigate cerebellar involvement in temporal and numerical discrimination by rats. Evidence that temporal discrimination is disrupted in humans and rats with cerebellar lesions suggests that the cerebellum is involved in interval timing processes. In rats these deficits appear to be limited to millisecond range timing (Clarke et al, 1997) and impaired temporal discrimination by cerebellar patients has also been interpreted this way (Ivry & Keele, 1989; Nichelli et al, 1996). In support of one prominent view regarding the

cerebellum and timing, this evidence has suggested that the cerebellum operates as an independent timing mechanism restricted to the millisecond range[8] (e.g., Ivry, 1996; Ivry & Keele, 1989).

When the same evidence is viewed within the context of the mode-control model of timing, however, another hypothesis presents itself which forms the basis for much of the work presented in this thesis. The cerebellum may be involved with a source of constant variance associated with the central timing processes. Nichelli (1994), for example, has already speculated that cerebellar damage might add noise to switch processes although he did not elaborate this contention. In Section 1.4.4 (Figure 1.8), simulation of a formal implementation of the mode-control model clearly showed that an increase in switch variance (noise) has far greater impact on variability in the millisecond range compared with the seconds range, a result that is consistent with the experimental evidence that only milliseconds range timing rather than seconds range timing is disrupted by cerebellar lesions in humans and animals (Clarke et al, 1997, Nichelli et al, 1996). Moreover, additional noise from any source of constant variability in timing is consistent with this result. Thus, an analysis of variability in timing provides formal support for the proposal that the cerebellum is involved with a source of constant variance, such as switch processes, in a distributed timing system responsible for interval timing in the range from milliseconds to several minutes.

The current extension of Gibbon and colleague's (Gibbon, 1991, Gibbon et al, 1984) analysis of variance in timing to counting (Section 1.4.3) also provides the rational for the novel examination of the impact of cerebellar lesions on numerical discrimination. A specific source of constant variance in timing are switch processes that paradoxically contribute to scalar variance during counting. The simulations in Section 1.4.4 showed that an increase in switch variance leads to an increase in overall variability in counting while having little impact on overall variability in seconds range timing. Thus, a comparison of the impact of cerebellar lesions on performance in seconds range timing and a concurrent numerical discrimination in rats provides a

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[8] Henceforth, the milliseconds range refers to durations less than 1 or 2 s because the most convincing evidence for cerebellar involvement in timing comes from NMR conditioning (Perret et al, 1993) where this appears to be an upper limit for acquisition of the CR.

test of the hypothesis that the cerebellum is involved with switch processes that are a specific source of constant variance in timing.

Another hypothesis of cerebellar involvement in timing has also been proposed within the context of the mode-control model. In contrast to the original researchers, Gibbon et al (1997) attribute the deficits found in cerebellar patients by Nichelli et al (1996) in the seconds range to disrupted central timing rather than impaired perceptual or non-temporal cognitive processes. On the basis of this interpretation, plus some preliminary work of their own, Gibbon et al (1997) have suggested that the cerebellar lesions disrupt processes associated with the memory or decision stages of the mode-control model. The simulations in Section 1.4.4 show that disruption of scalar sources of variance in timing, such as memory or comparator variance, results in a proportional increase in overall variability for timing over both the milliseconds and the seconds range, with the possible exception of very brief durations that are close to the threshold for timing. The same scalar sources of variance also have a proportional impact on overall variability for counting.

Chapter 3 examines three hypotheses of cerebellar involvement in timing and counting processes. The simulations in Section 1.4.4 clearly demonstrate the expected influence of cerebellar damage on discrimination performance under each of these hypotheses. Ivry's hypothesis predicts that millisecond range timing should be disrupted, but seconds range timing and counting performance should be unimpaired. Gibbon's hypothesis quite clearly predicts that millisecond range timing, seconds range timing, and counting performance should all be impaired. The hypothesis developed in this thesis in its most general form predicts that millisecond range timing should be disrupted whereas seconds range timing should be spared. The more specific form of this hypothesis, implicating switch processes as a locus for cerebellar involvement in timing, predicts deficits in counting performance as well as deficits in millisecond range timing with seconds range timing relatively unimpaired.

The specific aims of Chapter 3 were to investigate the effects of lesions to the cerebellar vermis and hemispheres on a seconds range temporal discrimination and a numerical discrimination (Part 1) and the acquisition of a millisecond range discrimination by the lesioned rats (Part 2). Chapter 4 extends the investigation of cerebellar involvement in timing by

examining the effects of cerebellar hemisphere lesions in rats trained on millisecond and seconds range discriminations preoperatively (Part 1). The rats were then trained and tested on two additional temporal bisection tasks in each time range to further explore the impact of cerebellar lesions on scalar and constant variance in timing (Part 2). Based on suggestions that the mesolimbic system may play a role in seconds range timing (Meck, 1988; Rammsayer, 1996), lesions to the NAC provided comparative lesions in Chapter 4.

As mentioned in Section 1.2.2, some important issues regarding the nature of numerical discrimination by rats had to be resolved before proceeding with the lesion work in Chapter 3. Careful consideration of the periodic event sequences used in previous work that provides empirical support for the mode-control model of counting and timing (Meck & Church, 1983; Roberts & Mitchell, 1994) raises the possibility that temporal cues associated with these stimuli, or the stimulus pattern itself, may have supported numerical discrimination. Numerical discrimination based on temporal cues or stimulus pattern undermines the concept of an event mode (Meck & Church, 1983) that is central to the current argument that additional constant variability in switch processes underlying timing should also disrupt counting. The concern that temporal cues might be confounded with number was pertinent because these cues may fall within the range of Ivry's millisecond timer. If these temporal cues supported numerical discrimination, cerebellar damage could disrupt numerical discrimination through impaired timing. The issue of stimulus pattern was also important because it has been proposed that the cerebellum functions as a sequence generator and detector (Braitenberg, Heck, & Sultan, 1997; Maill, 1997; Maill, Weir, Wolpert & Stein, 1993). If stimulus pattern supports numerical discrimination, cerebellar damage could disrupt counting through impaired sequence detection or pattern recognition.

In addition, the results of Roberts and Mitchell's (1994) experiment 1 and the initial experiment in Chapter 2 of the current thesis raised questions regarding the natural utility of counting in animals that were examined in the final experiment of Chapter 2. These issues related to numerical discrimination are discussed in more detail in the introduction to the second chapter where the primary aims were to obviate concerns that non-numerical cues might support

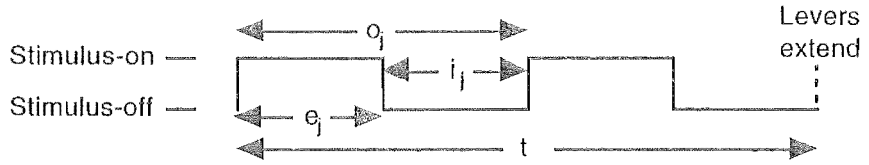
Chapter 2

Timing Ability and Numerical Competence in Rats

Chapter 2 presents a series of behavioural studies on timing and counting in intact rats that establish the validity of these procedures in examining the effects of cerebellar lesions on timing and counting in Chapter 3. The main focus of Chapter 2 is the concern that two nonnumeric cues associated with the periodic sequences used in previous animal psychophysical studies of counting (Fernandes & Church, 1982; Meck & Church, 1983; Roberts & Mitchell, 1994) may have supported the apparent numerical discrimination. These issues are relevant to the definition of numerical discrimination in animals as a formal demonstration of counting (Broadbent, Church, Meck, & Rakitin, 1993; Davis & Pérusse, 1988; Thomas & Lorden, 1993) and are addressed in the main part of this Chapter. Unexpected results in an initial replication of Meck & Church's (1983) Experiment 1, also prompted an additional experiment on the relative salience of time and number.

The main concern with previous studies of numerical discrimination that used sequential stimuli (Fernandes & Church, 1982; Meck & Church, 1983; Roberts & Mitchell, 1994) is that these periodic event sequences may have allowed the animals to base their discriminations on uncontrolled and unintended temporal attributes of the event sequence that were confounded with number. Many potential temporal cues to numerosity (Figure 2.1A), such as total sequence duration (t), event duration (ej), the interval between events or between event onsets (ij and oj, respectively) and the sum of these discrete intervals (Σij and Σoj; see Church & Meck, 1984) have been controlled in previous research. However, when a fixed number of identical events occur periodically, the ratios of the interval between event onset, event duration, and interevent duration to total duration remain constant, irrespective of total signal duration (respectively, $oj{:}t$, $ej{:}t$, and $ij{:}t$, collectively referred to as temporal ratio cues). As a consequence, these ratios

A



B

	Number of events	Onset duration	Total duration	Temporal ratio	Reinforced response
		o_j	t	o_j : t	
i) Compound signals					
	2	1	2	1:2	L
	8	1	8	1:8	R
ii) Number-relevant signals					
	2	2	4	1:2	L (Expt 2 & 4)
	3	1.33	4	1:3	—
	4	1	4	1:4	—
	5	0.8	4	1:5	—
	6	0.67	4	1:6	—
	8	0.5	4	1:8	R (Expt 2 & 4)
iii) Time-relevant signals					
	4	0.5	2	1:4	L (Expt 2 & 4)
	4	0.75	3	1:4	—
	4	1	4	1:4	—
	4	1.25	5	1:4	—
	4	1.5	6	1:4	—
	4	2	8	1:4	R (Expt 2 & 4)

iv) Unique standards (examples)

2 event	DS_{ratio}	$DS_{pattern}$	8 event	DS_{ratio}	$DS_{pattern}$
	0	0.7		0.2	0.4
	0.4	0.6		0.3	0.5
	0.6	1.6		0.4	0.4
	0.5	1.3		0.5	0.5
	2.1	1.8		0.6	0.4
	2.1	1.5		0.7	0.6

Figure 2.1. Panel A: Diagram showing the temporal attributes of the signal; t = total signal duration; oj = event onset duration; ej = event duration; ij = interevent duration. Panels B i to iii: Sound sequences used by Meck and Church (1983) in their Experiments 1 and 2 and the periodic signals used in Experiments 1 and 2 of the current study. The compound signals were used in Experiment 1 only. L and R refer to the reinforced lever press associated with the signals in both studies; Expt = experiment. Panel B iv: Examples of the unique signals used in Experiments 2 and 3; DSratio = ratio deviation score; DSpattern = pattern deviation score.

covary with the number of events and so constitute a potential confound that has been overlooked. For example, if animals are trained to discriminate a compound two-event, 2 s (2e/2s) signal from a compound eight-event, 8 s (8e/8s) signal, the temporal ratios 1:2 and 1:8, respectively, are also confounded with total duration and number of events. During testing, when time and number are unconfounded by holding one of these dimensions constant while the other varies, temporal ratio nonetheless remains confounded with number (Figure 2.1B). Thus, a parsimonious explanation as to why the psychophysical functions generated by the number-relevant and time-relevant signals superpose is that the computation of a temporal ratio, rather than a counting process such as the event mode, determines the psychophysics of the number-relevant curve. In fact, the computation of a ratio between magnitudes, temporal or otherwise, is central to the decision stage of the mode-control model (Church & Meck, 1984; Gallistel, 1988, 1990; Meck & Church, 1983). In addition, Fetterman, Dreyfus, & Stubbs, (1989, 1993) have shown that pigeons can perform temporal discriminations based on ratio comparisons just as accurately as those based on relative duration.

The second concern arises from the fact that relatively few sequence patterns are routinely used as the exemplars of a particular numerosity. In some experiments, the periodic standards are the same during training and testing (e.g., Experiment 2, Meck & Church, 1983; Experiments 2-5, Roberts & Mitchell, 1993) so that the animals may have learned to respond to a signal by matching it to a specific pattern stored in reference memory (Thomas & Lorden, 1993). In this instance, stimulus generalization based on pattern recognition may underlie the curvilinear gradient of the psychophysical function for number. Even when the duration of the periodic sequence representing a particular numerosity changes between training and testing, as is the case when compound standards are used (Experiment 2.1 in this chapter; Experiment 1, Meck & Church, 1983; Experiment 1, Roberts & Mitchell, 1993), a somewhat flexible form of template matching, analogous to rescaling the signal diagrams in Figure 2.1B, may have supported numerical discrimination. Davis and Pérusse (1988) labelled this process "rhythm" (see also von Glasersfeld, 1993), and in human work its flexibility has been demonstrated where tempo, or temporal pattern, has been slowed down or sped up without changing perceived rhythm (e.g.,

Handel, 1993). Thus, various kinds of template matching processes may provide the basis for numerical discrimination whenever periodic signals are used.

The distinction between the event mode and temporal ratio or pattern recognition as the mechanism of enumeration is important because only the event mode meets the main criteria for counting set by Gelman and Gallistel (1978). Temporal ratio and pattern recognition accurately represent the numerosity of the entire signal, as required by the cardinal principle, but there is no tagging of discrete events as required by the one-one principle and the stable-order principle (Broadbent et al., 1993).

Temporal ratio and pattern recognition are problems that arise when only a few periodic event sequences are used. The solution to both problems, then, is to vary the duration of the internal temporal components of the signal so that a unique event sequence for each signal is presented on every trial (Figure 2.1B iv). If either temporal ratio or pattern recognition provides the basis for numerical discrimination, then a change from periodic signals to unique signals should markedly disrupt number discrimination. The purpose of the main experiment (Experiment 2.2) was to test this prediction. Experiment 2.3 compared acquisition and asymptotic performance of numerical and temporal discriminations by naive rats when only unique signals were used throughout training and testing.

Prior to investigating the effects of unique signals, however, Experiment 2.1 aimed to replicate Meck and Church's (1983) Experiment 1. On the basis of their results Meck and Church (1983) concluded that counting is natural for rats and that they are equally likely to use either temporal or numerical cues when both are available (see also Capaldi & Miller, 1988). Conversely, Davis (1993; Davis & Bradford, 1986; Davis & Memmott, 1983; Davis & Pérusse, 1988) has maintained that numerical discrimination is difficult for animals to learn and that they do so only as a last resort, in the absence of more salient cues. These opposing views were examined in Experiment 2.4.

Experiment 2.1

The procedure for this experiment was identical to that described by Meck and Church (Experiment 1, 1983) except that additional training was given prior to the second test session to maintain steady-state performance. The rats were trained to choose between two levers with two sequences of sound events where both number of events and sequence duration predicted the same reinforced choice. Once consistently accurate discrimination was established, the relative control of time and number was tested by holding one dimension constant at an intermediate value while the other attribute varied between the values used during training.

Method

Animals

The animals were 6 experimentally naive female Wistar rats (*Rattus norvegicus*) about 90 days old at the start of training. The rats were maintained at 80-85% free-feeding weight throughout the experiment with water supplied ad libitum. A 12:12-hr light-dark cycle was maintained in the colony room, and the rats were trained and tested at the same time each day during the dark cycle.

Apparatus

Six operant boxes measuring approximately 28 x 20 x 23 cm were used. In each box, two retractable aluminium levers projected through the front panel on either side of a food cup. The levers were 2 cm long x 3 to 5 cm wide and were located 10 cm (BRS/LVE Model 123-05, Beltsville, MD; Boxes 1-3), 8.5 cm (Coulbourns Model E23-05, Allentown, PA; Box 4), and 8 cm (MED Associates ENV-112, St Albans, VT; Boxes 5 and 6) above the floor. A condensed-milk solution reinforcer (0.12 ml) was delivered at floor level by a mechanical dipper

(Gerbands G5600 B-LH,Arlington, MA; Boxes 1-4) or a dripper (Lafayette 80201, Lafayette, IN; Boxes 5 and 6). Each box was lit by a houselight (3-x 80-mA bulbs) located at the center of the roof. A white noise generator (Lafayette 15012) was used to deliver white noise of about 82 dB (re 20 mN/m^2; Precision Sound Level meter, Brüel and Kjaer, type 2235, A scale, Skodsberg, Denmark) above background level through a 4-in. (10.2 cm) speaker mounted on the roof of each lever box. Each box was itself enclosed in a sound-attenuating chamber with a ventilation fan at the rear that also helped to mask extraneous sound. All the chambers were in a darkened room and connected to an IBM-compatible computer, located in a separate room, by a MED Associates interface. MED-PC Medstate notation v1.43 (1988) software was used to control the experimental sessions and record data.

Procedure

Pretraining. Each rat received at least two sessions of training with levers and reinforcement. The condensed-milk reinforcer was delivered every 60 s and after each lever press. The session began with the insertion of the left lever; after 10 responses the left lever retracted and the right lever was inserted for 10 responses. This alternation continued until the rat had responded on each lever 60 times or when 30 min had passed. All sessions began with illumination of the houselight that remained on until the session terminated.

Training (Days 1-16 and 18-22). The signals used in this experiment were repeating periods of sound-on and sound-off identical to those used by Meck and Church (1983). During training, the sound-on and sound-off periods were both 0.5 s. The initial onset of white noise signified the beginning of a signal and the final sound-off was terminated with the insertion of both levers. The rats were reinforced for pressing the left lever following a sequence of two sounds with a total duration of 2.0 s. A response on the right lever was reinforced following a sequence of eight sounds with a total duration of 8.0 s (Figure 2.1B i, compound standards). On each trial, one of the two signals was presented randomly with a probability of 0.5. If the rat made the correct response, condensed milk was delivered immediately; if the rat made an incorrect response, no reinforcer was delivered. Both levers were retracted when either lever

was pressed or after an interval of 8.0 s with no response. Intertrial intervals were 5.0 s plus a randomly distributed duration with a mean of 35.0 s (range = 0.1 - 69.9 s). Sessions were conducted daily and lasted 3 hrs. The type of response and its latency was recorded for each trial. During the first 5 days of training a signal that was followed by an incorrect response was repeated on the next trial (correction procedure).

Testing for control by time and number (Days 17 and 23). The conditions of training were maintained except that each standard signal was presented with a probability of 0.25 on each trial. On the remaining trials, two sets of 6 probe signal were unreinforced. For one set, total signal duration was held constant at 4.0 s, and the number of sounds varied between 2, 3, 4, 5, 6, and 8 (Figure 2.1B ii, number-relevant signals). For the other set, the number of sounds was held constant at four, and total duration varied between 2.0, 3.0, 4.0, 5.0, 6.0, and 8.0 s (Figure 2.1B iii, time-relevant signals). Sound-on duration equalled sound-off duration and was determined by the total duration of each signal. The 12 probe signals were presented with equal probability in a pseudorandom manner with a run of consecutive unreinforced signals limited to 4. The two test sessions were separated by 5 days of training because Meck & Church (1983) reported that responding to time and number was disrupted when a second test session immediately followed the first.

Data Analysis

Responses with latencies greater than 3 s are poorly controlled by the reinforced dimension (e.g., Maricq & Church, 1983) and were excluded in any figures or calculations presented here. Training data are reported as percentage correct, and test data are reported as proportion of responses on the right lever ($P[R]$). The following equation was fitted to the mean test data for each rat by using a weighted least squares procedure:

$$P(R) = p(A)p(R|A) + p(\sim A)p(R|\sim A), \tag{2.1}$$

where $p(R|A)$ was a logistic approximation of the cumulative normal distribution that provided the mean and standard deviation used to estimate the point of subjective equality (PSE), the difference limen (DL), and Weber fraction (DL/PSE). The PSE represents the stimulus value at

which the rat is equally likely to choose left or right levers, the mean of the logistic function, given the assumption of normality. The DL is a measure of sensitivity to differences between stimuli that is independent of overall stimulus control (see Blough, 1996) and is defined as half the range of values between the signal value that has a 0.25 probability of eliciting a right response and the signal value that has a 0.75 probability of eliciting a right response, or 0.675 of the standard deviation (cf. Fetterman & Killeen, 1992). The probability of attending to the stimulus dimension is $p(A)$ and it is assumed that when animals do not attend to the stimulus dimension the probability of a right lever response is a constant bias $p(R|\sim A)$ (Heinemann & Chase, 1970; Meck & Church, 1983). Thus, Equation 2.1 has four free parameters and provides a bias-free estimate of overall performance, the mean, and standard deviation. It also provides an improved goodness - of - fit compared with the logistic function alone.

For this experiment and all subsequent experiments, mean values are reported plus or minus the standard error of the means, and the significance level for all statistical tests was set at $p < 0.05$ (two-tailed), except for the deviation scores in Experiment 2, which required a one-tailed test.

Results and Discussion

During training all rats became extremely accurate at making the compound time and number discrimination. The mean percentage correct over the last 10 days of training was 97% (SEM = 1.0), and 97% (SEM = 0.6) for the 2e/2s and 8e/8s signals, respectively, and performance did not differ between Days 12 to 16 and Days 18 to 22. The mean percentage of trials discarded by the 3.0 s latency criterion was 6% (SEM = 1.3) across these training sessions and 5% (SEM = 1.8) across the test sessions (Days 17 & 23).

The main focus of Experiment 2.1 was performance in the two test sessions and the findings were clear: After training with a pair of signals in which total duration and number of sound events were confounded, the rats accurately discriminated signal duration (time) when number was held constant. However, when time was held constant so that only number predicted the reinforced choice, the rats continued to respond on the basis of time and appeared

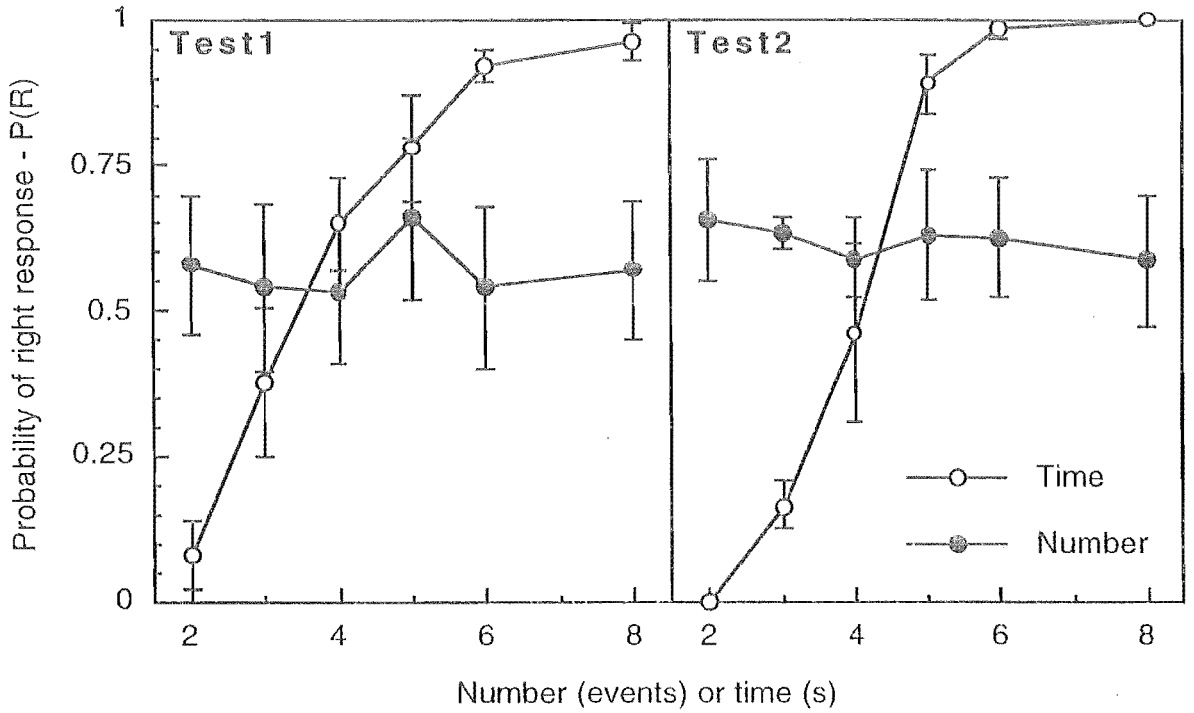


Figure 2.2. Mean probability of a right response (±SE) as a function of number or time for each test session in Experiment 2.1.

to have ignored the numerical cues completely (Figure 2.2). A Session x Signal (time vs. number) x Length (2 to 8) analysis of variance (ANOVA) yielded a significant effect of length, $F(5, 25) = 16.6$, but not for signal or session, $F(1, 5) < 1.0$. As expected, there was a significant Signal x Length interaction, $F(5, 25) = 18.6$, as a consequence of the flat curve for number. Simple main effects confirmed a significant control of choice behaviour by time, $F(5, 25) = 42.7$ but not by number, $F(5, 25) < 1.0$.

Equation 2.1 accounted for a mean 95% (SEM = 1.8) of the variance in the time-probe data for each rat, with no systematic deviations from the predicted data points. It provided a mean PSE of 3.71 (SEM = 0.18), a mean DL of 0.65 (SEM = 0.06), and a mean Weber fraction of 0.18 (SEM = 0.03; see Table 1). These psychophysical parameters for time estimation by rats were comparable to those reported previously for similar bisection procedures (eg., Maricq, Roberts & Church, 1981; Meck & Church, 1983; Meck, Church, & Olton, 1984), although the PSE and DL were a little shorter here. For the number-probe data, Equation 2.1 could not be fitted and parameters comparable to those estimated for time could not be obtained. However, the mean

position bias ($p[R|\sim A]$) for number was calculated by using the computational formula of Heinemann, Avin, Sullivan and Chase (1969; see also Heinemann and Chase, 1970) which revealed that a slight bias was evident, 0.61 (SEM = 0.10) and 0.62 (SEM = 0.10), in each test session, respectively. It is unlikely that this bias obscured any control by number, as the variability in performance across length for number was similar to that found with the 4e/4s probe signal. When straight lines were fitted to the number data for each rat in each test session, the slopes did not differ significantly from zero, $t(5) < 1.0$ (range = -0.05 - 0.06).

The current findings dramatically conflict with those reported by Meck and Church (Experiment 1, 1983) in which both the temporal and numerical attributes of the compound signals gained strong control over choice behaviour in their rats. There is no obvious explanation for this discrepancy because the details of the two experiments were almost identical. In addition, although one other study claims to have replicated Meck & Church's (1983) results, the General Discussion elaborates how these data from pigeons (Roberts & Mitchell, 1994) are actually more consistent with the current findings.

Table 2.1
Mean Estimates of Parameter Values for Psychophysical Functions Obtained in Experiments 2.1, 2.2, and 2.3

	Experiment and signal	$p(A)$	$p(R\|\sim A)$	PSE	DL	WF	ω^2
1							
	Time-periodic	0.93	0.31	3.71	0.65	0.18	0.95
2							
	Time-periodic	0.96	0.17	3.56	0.74	0.21	0.91
	Time-unique	0.98	0.19	3.82	0.85	0.23	0.95
	Number-periodic	0.73	0.45	3.47	0.72	0.21	0.96
	Number-unique	0.83	0.30	3.74	1.04	0.28	0.97
3							
	Time-unique	0.92	0.14	4.02	0.83	0.20	0.95
	Number-unique	0.84	0.25	4.07	1.22	0.30	0.93

Note. $p(A)$ = probability of attention; $p(R|\sim A)$ = probability of a right response given inattention; PSE = point of subjective equality; DL = difference limen; WF = Weber fraction; ω^2 = variance explained.

Experiment 2.2

In Experiment 2.1, number failed to gain control of choice behaviour after training with compound signals where both time and number were accurate cues to reinforced lever choice. In Experiment 2.2, the first aim was to train the rats to accurately discriminate between two and eight events by using separate time-relevant and number-relevant standards and then to testing with the unreinforced probe signals (Figure 2.1B) so that the rats sensitivity to time and number could be compared.

Until this point, the signals used in Experiments 2.1 and 2.2 had been the same as those used in previous psychophysical bisection studies of numerical discrimination (Meck & Church, 1983; Roberts & Mitchell, 1994; Roberts, Macuda, & Brodbeck, 1995) in a fundamental way. The temporal structure of each standard was both periodic and invariant across presentations, leaving two potential confounds with number: temporal ratio and pattern recognition. After testing with the periodic probe signals in Experiment 2.2, training with periodic standards was resumed for five sessions and then the temporal pattern of each signal was changed abruptly. On every trial, the temporal pattern for each number-relevant or time-relevant signal was randomly generated; only the number of events and the total duration remained constant. If the rats' were using a temporal ratio or pattern recognition for number discrimination, the change to these *unique* standards should severely disrupt discrimination performance on number but not on time. Also, the rats performance should be better with signals where the temporal ratio or pattern of the unique number standard was most similar to the corresponding periodic number standard. Finally, each rat's sensitivity to changes in time and number with unique signals was evaluated by testing with intermediate unique probe signals.

Method

Animals and Apparatus

The animals and the apparatus were the same as in Experiment 2.1.

Procedure

Training with periodic signals (Days 1-22 and 26-30). During training, the two number standards had a total duration of 4.0 s with either two or eight sound-on events, whereas the two time standards had a total duration of 2.0 s or 8.0 s with the total number of events held constant at four. A left-lever response was reinforced when the number of events was two or the total duration was 2.0 s, and a right-lever response was reinforced when the number of events was eight or the total duration was 8.0 s (see Figure 2.1B ii and iii). These four periodic signals were presented pseudorandomly with equal probability and without any correction trials.

Testing with periodic signals(Days 23, 24, and 25). The four periodic standards were presented pseudorandomly with equal probability (0.125) on half the trials, and correct responses were reinforced. On the remaining trials, eight probe signals were presented pseudorandomly with equal probability, and all responses were unreinforced. Four periodic number probes held total signal duration constant at 4.0 s while the number of events varied between 3, 4, 5, and 6. The other four periodic time probes held the number of events constant at four while total duration varied between 3.0, 4.0, 5.0, and 6.0 s.

Training with unique signals (Days 31-41). The conditions of training were the same as described for days 26-30 except that on every trial the temporal structure of each signal was determined by randomly varying every sound-on duration and every sound-off duration, constrained only by a minimum sound-on duration of 100 ms, a minimum sound-off duration of 200 ms, and the total duration of the signal.

Testing with unique signals (Days 42, 43, and 44). The conditions of testing were identical to those on Days 23, 24, and 25, except that all the signals now had sound-on and sound-off durations that varied randomly for each probe signal in the manner described above.

Data Analysis.

Equation 2.1 was fitted to the data from test days and the PSE, DL, and Weber fraction estimated as in Experiment 2.1. For unique number standards only, the topography of errors made was also examined. The similarity in temporal ratio and signal pattern of each unique standard to its corresponding periodic standard was calculated for each of the unique number standards presented over the 5 days immediately after the change to unique standards (Days 31-35). A ratio deviation score (ie. $DS2_{ratio}$ for 2e/4s signals, $DS8_{ratio}$ for 8e/4s signals) provided a measure of deviation in terms of oj:t ratio, and a pattern deviation score (ie. $DS2_{pattern}$ for 4e/2s signals, $DS8_{pattern}$ for 4e/8s signals) provided a measure of deviation in terms of signal pattern. Both scores were derived from the following general formula:

$$DS = \sqrt{\sum_{j=1}^{j=n}(D - d_j)^2} \qquad (2.2)$$

For the $DS2_{ratio}$ and $DS8_{ratio}$, D is the event onset duration of the periodic standard (2.0 s or 0.5 s), dj is the unique signal event onset duration (oj), and n is the number of events. For the $DS2_{pattern}$ and $DS8_{pattern}$, D is the duration equal to sound-on or sound-off duration of the standard signal (1.00 s or 0.25 s), dj is the unique signal sound-on (ej) or sound-off (ij) duration, so that j is odd for sound-on and even for sound-off, and n is equal to twice the number of events (see Figures 2.1A and 2.1B iv). The relationship between percentage correct and these measures was determined for each rat by using product-moment correlations.

Results and Discussion

Periodic Signals

The rats maintained their already accurate performance on the temporal discrimination and showed a gradual improvement on the number discrimination that stabilised after about 15 days of training. Thus, the rats were able to learn the numerical discrimination when trained with the explicit number-relevant standards (see Figure 2.3A). Although performance on the numerical discrimination was highly accurate by the end of training, it was nonetheless significantly poorer than that on the temporal discrimination. The mean percentage correct averaged over the last 5 days (Days 18-22) of standard signal training was 96% (SEM = 1.2) and 96.0% (SEM = 0.7) for the 2.0 s and 8.0 s standards, respectively, compared with 85% (SEM = 4.3) and 90% (SEM = 1.4) for the two- and eight-event standards, respectively. A Days (18-22) x Signal (time vs. number) x Length (2 - 8) ANOVA revealed a significant effect of signal, $F(1, 5) = 17.3$, only. The mean percentage of trials excluded under the 3.0 s latency criterion was 5% (SEM = 3.2) during training and 5% (SEM = 2.3) during testing.

For test days, a Signal x Length ANOVA yielded a significant effect of length, $F(5, 25) = 83.3$, but not of signal, $F(1, 5) < 1.0$ (see Figure 2.3B). An important finding, however, was the significant Signal x Length interaction, $F(5, 25) = 6.1$ reflecting poorer performance on the number discrimination compared with the temporal discrimination. The differences in the performance between time (s) and number were significant for lengths 2, 6, and 8, $F(1, 2) > 10.4$. As expected, both time, $F(5, 25) = 65.1$, and number, $F(5, 25) = 49.0$, had gained a significant control of choice behaviour across signal length.

Unique Signals

The most striking finding of Experiment 2.2, immediately apparent from Figure 2.3A, was that an abrupt change from the periodic standards to the unique standards had no effect on the extremely high accuracy with which the rats performed either the numerical discrimination or the

temporal discrimination. A Type (periodic vs. unique) x Signal (time vs. number) x Length (2 or 8) ANOVA on the data from the training sessions immediately before and immediately after the change to unique signals (Days 30 and 31) supported these observations. The main effect of signal was significant, $F(1, 5) = 124.2$, as expected, but there was no evidence of a main effect of type, $F(1, 5) < 1.0$, or of Type x Signal interaction, $F(1, 5) < 1.0$. Analysis of the data from the 5 sessions preceding and following the change to unique signals (Days 26-35) revealed the same pattern of results, with no main effect of type, $F(1, 5) = 2.65$, or of Type x Signal interaction, $F(1, 5) = 2.61$. This 4-way ANOVA, including the five sessions after the change to unique signals, was the minimum required for meaningful analysis with the deviation measures reported below. The mean percentage trials excluded under the 3.0 s latency criterion was 5% (SEM = 0.4) and 6% (SEM = 0.5) for the 5 days before and after the change, respectively, which is important confirmation that the rats' general level of responding was also unaffected. The increase in standard error toward the end of unique-signal training reflects a bias to respond right by one rat only and was related to a temporary equipment problem.

The data from the test days (Days 42, 43, and 44) with unique signals was similar to that obtained by using periodic signals (see Figure 2.3C). A Signal (time vs. number) x Length (2 to 8) ANOVA revealed a significant effect of length, $F(5, 25) = 144.3$, but not of signal, $F(1, 5) < 1.0$. As before, the poorer performance on number compared with time was reflected by a significant Signal x Length interaction, $F(5, 25) = 8.1$, with significant differences between time (s) and number for lengths 2, 6, and 8, $F(1, 2) > 7.8$.

Parameter Estimates for Periodic and Unique Signals

Equation 2.1 accounted for 91% (SEM = 3.4) and 96% (SEM = 1.5) of the variance for the periodic time and number data, respectively, and 95% (SEM = 2.3 and 97% (SEM = 0.8 of the variance for the unique time and number data, respectively. The mean parameters estimated from the fitted curves, shown in Table 2.1, were analyzed by two-way (Type x Signal) ANOVAs. Performance during testing, as reflected by p(A), did not differ for periodic and unique signals, $F(1, 5) = 1.6$, but was poorer on number compared with time; signal,

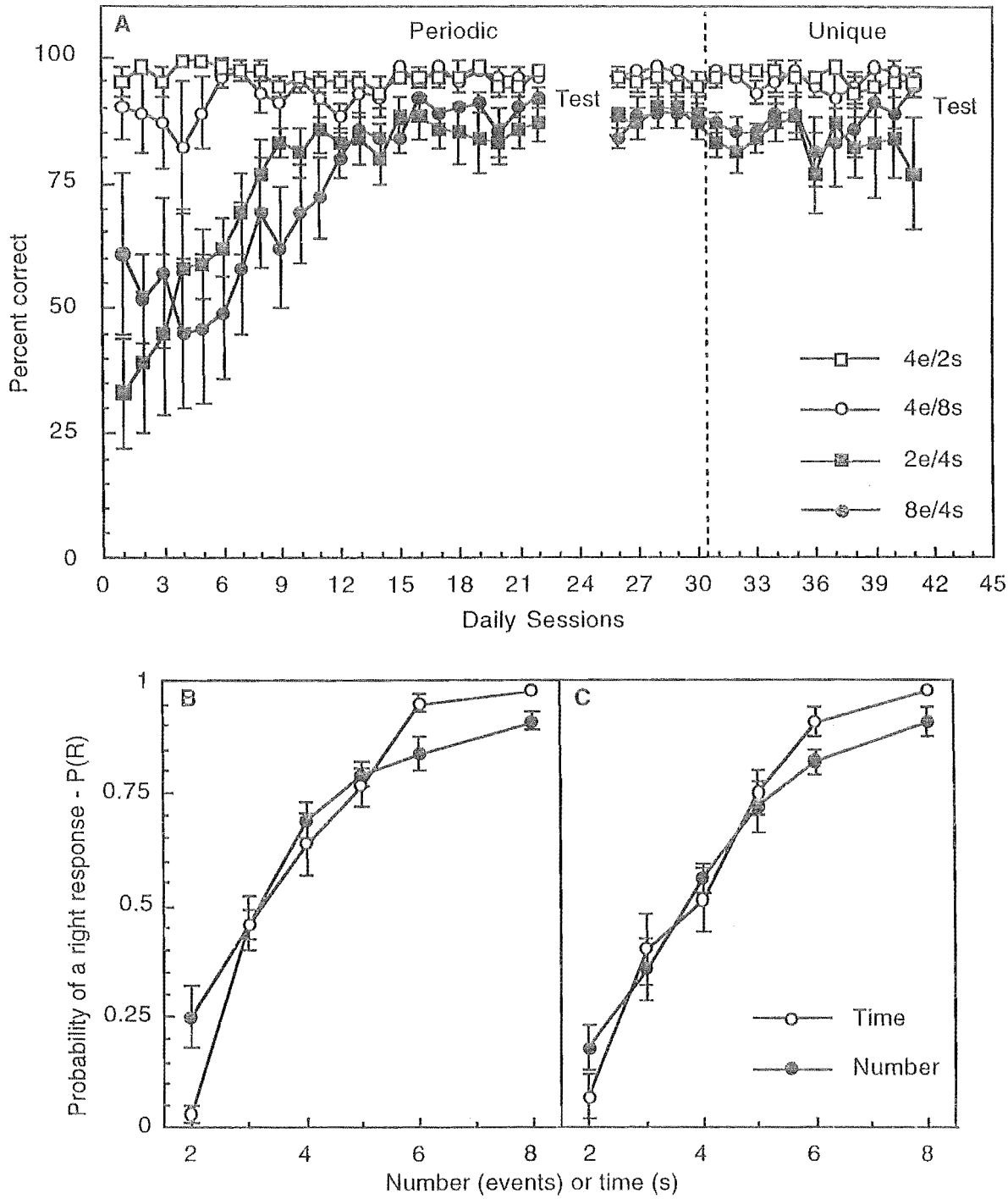


Figure 2.3. Panel A: Percentage correct (±SE) as a function of training sessions in Experiment 2.2 for number-relevant signals (2e/4s [two-event, 4-s] and 8e/4s [eight-event, 4-s]) and time-relevant signals (4e/2s [four-event, 2-s] and 4e/8s [four-event, 8-s]). The change from periodic signals to unique signals occurred after the 30th session as indicated by the vertical dashed line. Panel B: Mean probability of a right response (±SE) as a function of number or time with periodic signals in Experiment 2.2. Panel C: Mean probability of a right response (±SE) as a function of number or time with unique signals in Experiment 2.2.

$F(1, 5) = 20.9$; Type x Signal, $F(1, 5) = 1.2$, *NS*. Although there appeared to be a stronger bias, p(Rl~A), toward the 2e/2s lever for number compared with time, this difference was not significant, $F(1, 5) = 3.9$, and was stable across signal type, $F(1, 5) < 1.0$. For the estimates PSE, DL, and Weber fraction there were no significant main effects and no significant interaction, $F(1, 5) < 2.8$. However, for number both the DL and the Weber fraction increased consistently (for 5 out of 6 rats) with the change from periodic to unique test signals (0.72 to 1.04 for mean DL, and 0.21 to 0.28 for Weber fraction) suggesting some decrease in the sensitivity to number with unique signals, although neither of these changes reached statistical significance.

Deviation Scores for Unique Number-Relevant Signals

The range of deviation scores was more restricted for eight-event signals because of inherent temporal constraints. For this reason scores, were sorted into six equal-sized bins across each measure. The range of these bins was determined by the constraint that each contained at least six scores per rat. Scores outside this range were treated as outliers and excluded. The range and percentage of outliers for each measure was as follows: $DS2_{ratio}$, 0-2.12, 0%; $DS8_{ratio}$, 0.2-0.7, 2%; $DS2_{ratio}$, 0.1-2.1, 1%; $DS8_{pattern}$, 0.3-0.7, 2%. For the two-event signal, 17% of $DS2_{ratio}$ scores were equivalent to that of the periodic standard. The mean percentage correct over the first 5 days of unique signals as a function of each deviation measure and the correlation coefficients for each rat are shown in Figure 2.4. Overall, there was a significant negative correlation across rats for $DS2_{ratio}$ (-0.39) and $DS2_{pattern}$ (-0.46) but not for $DS8_{ratio}$ and $DS8_{pattern}$. There was consistency between the correlations for $DS2_{ratio}$ and $DS8_{ratio}$ for only 3 of the 6 rats. Although the results suggest that there was some influence of unique signal similarity to the previously presented periodic standards, a marked and consistent decrement in performance with increasing deviation score would be expected if either temporal ratio or pattern recognition formed the basis for numerical discrimination. Overall, however, discrimination was highly accurate even when unique signals were quite different from the periodic standard. Percentage correct for extreme deviation scores dropped below 80%

($DS2_{ratio}$) and 70% ($DS2_{pattern}$) for only 2 rats. This suggests that neither temporal ratio nor pattern recognition underlies the mechanism for numerical discrimination, although irregularity in the sequences tended to disrupt performance in some rats.

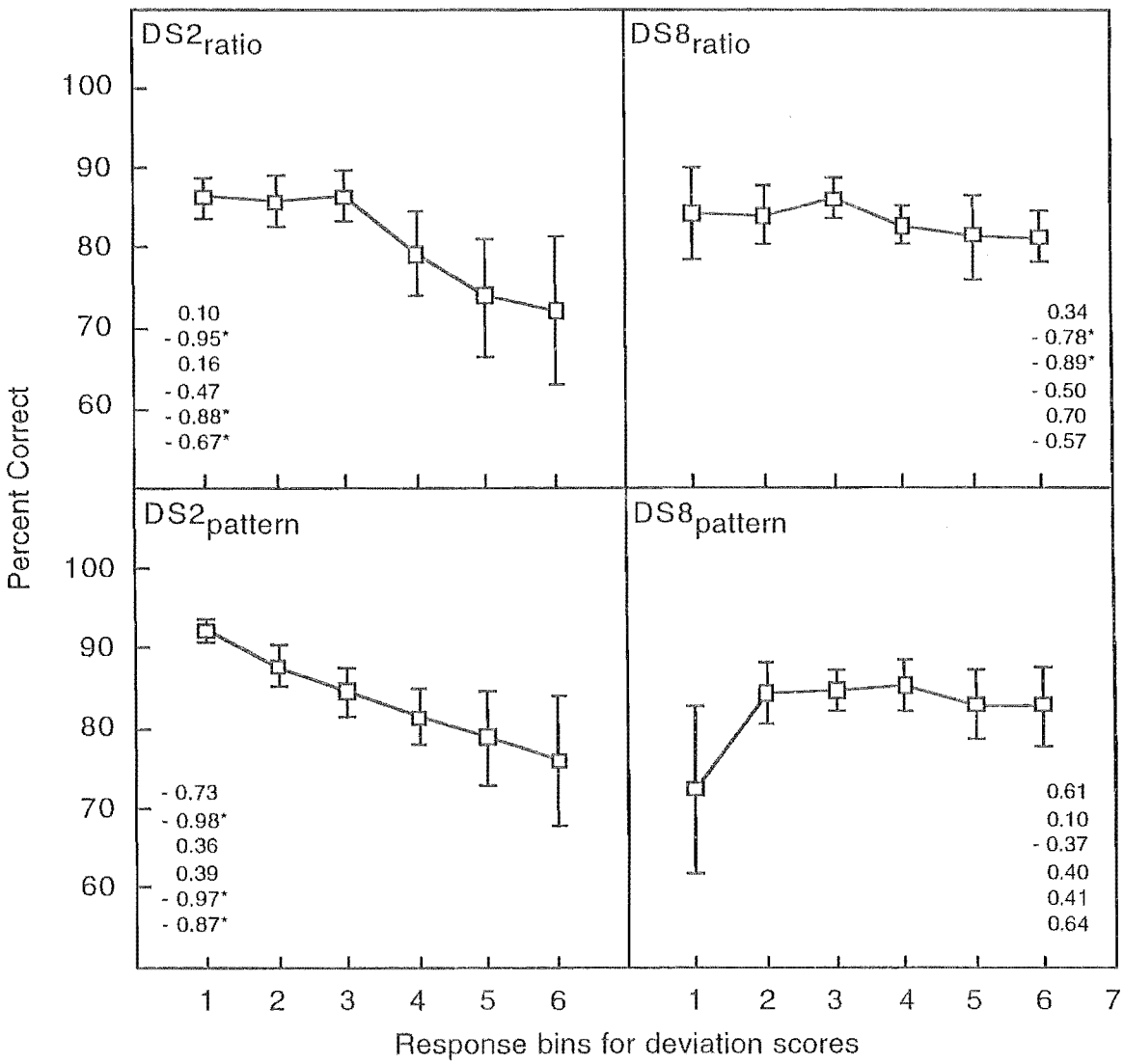


Figure 2.4. Percentage correct (±SE) as a function of ration deviation score (DS_{ratio}; top) and pattern ratio score ($DS_{pattern}$; bottom). Inset shows the correlation coefficients for individual animals. An asterisk denotes a significant correlation.

Experiment 2.3

Contrary to the study by Meck and Church (1983), discrimination between numerical standards in Experiment 2.2 was poorer than between the temporal standards. There was also some indication that the rats' sensitivity to time and number might be different when the events to be counted occurred at irregular intervals. These findings could reflect a general advantage in interval timing over enumeration, or the results might have been a consequence of rats having learned the temporal discrimination first. Thus, Experiment 2.3 compared acquisition and psychophysical functions of numerical and temporal discrimination by naive rats trained concurrently with unique time and unique number standards.

Method

Animals and Apparatus

The animals were 32 experimentally naive female Wistar rats about 120 days old at the start of training. The rats were maintained at 80-85% of their free-feeding weight throughout with water supplied ad libitum. Housing, test conditions, and apparatus were the same as those used in Experiments 2.1 and 2.2 except that two additional operant boxes, identical to Boxes 5 and 6, were added.

Procedure

Pretraining. Pretraining was the same as in Experiment 2.1.

Training (Days 1-52). Training was the same as that for unique standards in the second part of Experiment 2.2, with the addition of a correction procedure that lasted for at least 5 days

(discontinued when a rat reached a criterion of 70% correct, applied separately to time and number). Sessions were conducted daily and lasted 3 hr.

Testing (Days 53, 54, and 55). The conditions of testing were identical to those with unique signals in Experiment 2.2.

Results and Discussion

As is clear from Figure 2.5A, both rate of acquisition and asymptotic performance was poorer for unique number standards than for unique time standards. The finding that rats had difficulty processing numerical information was reinforced by the fact that 7 rats (23% of the sample) learned to discriminate between 2.0 s and 8.0 s (91% [SEM = 0.02] and 90% [SEM = 0.01] percentage correct, respectively, for these rats) but failed to reach the 70% correct criterion for the number discrimination despite 52 days of training. All data from these rats were excluded from any figures or subsequent analysis. For the rats that acquired the number discrimination, the rate of learning for this discrimination was much slower than the rate of learning for the temporal discrimination, which was confirmed by a Signal x Length x Block (4 sessions per block). The important findings were a main effect of signal, $F(1, 24) = 163.4$, reflecting the far better performance on the temporal compared with number discrimination, and a significant Signal x Block interaction, $F(12, 228) = 20.8$, reflecting the more rapid acquisition of the temporal discrimination. A significant Signal x Length x Block interaction, $F(12, 228) = 4.4$, was a consequence of a larger difference in rate of discrimination learning between the two-event and the eight-event standards compared with the difference in rate of discrimination learning between the 8.0 s and the 2.0 s standards. Asymptotic performance at the completion of training for the numerical discrimination was lower than asymptotic performance for the temporal discrimination even though the rats had been trained explicitly with both number-relevant and time-relevant standards concurrently from the onset of training. However, most of the rats were able to learn the numerical discrimination, which replicates the finding in Experiment 2.2 that regularity in event sequence is not necessary for number discrimination by rats.

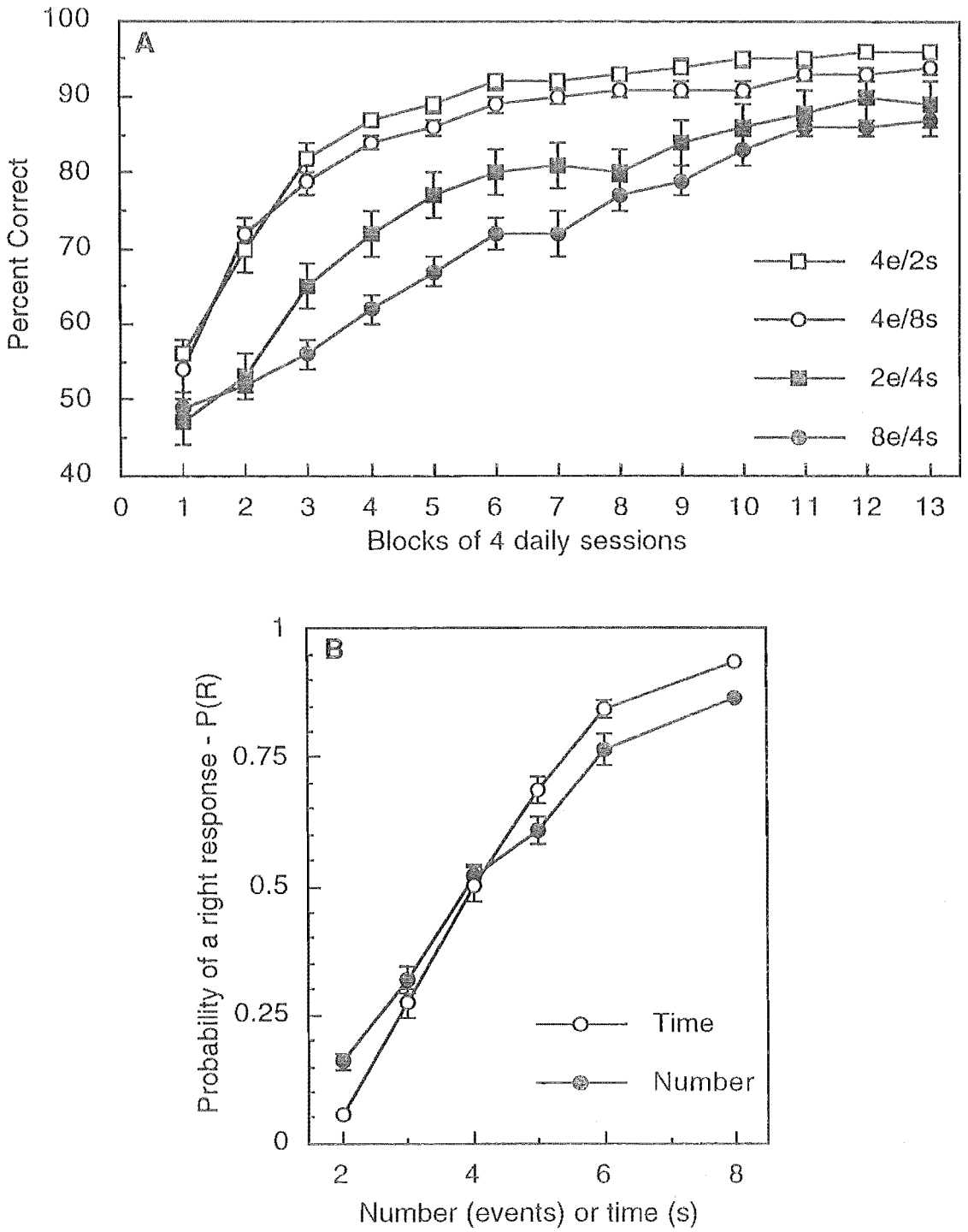


Figure 2.5. Panel A: Percent correct (±SE) during training of naive rats with unique number-relevant signals (2e/4s [two-event, 4-s] and 8e/4s [eight-event, 4-s]) and unique time-relevant signals (4e/2s [four-event, 2-s] and 4e/8s [four-event, 8-s]) in Experiment 2.3. Panel B: Mean probability of a right response (±SE) as a function of number or time in Experiment 2.3.

The psychophysical curves generated by the probe-signal data (see Figure 2.5B) supported the findings of Experiment 2.2 concerning the relative ability of rats to process temporal and numerical information. A Signal x Length ANOVA revealed a significant main effect of length, $F(5, 120) = 404.2$, but not of Signal, $F(1, 24) = 1.3$. Notably, the significant Signal x Length interaction, $F(5, 120) = 10.3$, was repeated, reflecting poorer performance on the number discrimination with significant differences occurring again at lengths 2, 6, and 8. Equation 2.1 explained a mean 96% (SEM = 0.9) and 93% (SEM = 1.4) of the variance for time and number, respectively. The bias parameter, p(Rl-A), was 0.14 (SEM = 0.05) for time and 0.25 (SEM = 0.06) for number, t(24) = 1.4, *NS*, indicating that there was an equal bias toward the 2e/2s lever for both time and number (see Table 1). The PSEs were also the same for time and number, 4.02 (SEM = 0.10) and 4.07 (SEM = 0.14), respectively, t(24) < 1.0. However, both DL and Weber fraction for time, 0.83 (SEM = 0.05 and 0.20 (SEM = 0.01), respectively, were significantly lower than the corresponding values for number, 1.22 (SEM = 0.08) and 0.30 (SEM = 0.02), respectively; t(24) = 4.58 for the DL, t(24) = 4.61 for the Weber fraction. The psychophysical functions were similar to those obtained for unique signals in Experiment 2.2, suggesting that the difference in performance between time and number under these conditions is not a consequence of prior experience. The fact that the DL and the Weber fraction were larger for number compared with those for time confirmed a trend that was evident in Experiment 2.2 and suggests that rats are less sensitive to changes in numerosity than to changes in time when events occur at irregular intervals. This difference may be due to the additional demands placed on the counting mechanism when events occur at irregular intervals, a competition for attentional resources (Mackintosh, 1975; Roberts & Mitchell, 1994), or a combination of both.

Experiment 2.4

This experiment directly investigated the last-resort hypothesis by testing the prediction that even animals that have been trained to respond on the basis of number will not do so if other accurate cues to reinforcement are available (Davis & Memmott, 1983). Rats were presented

with ambiguous probe signals (2e/8s; 8e/2s) in which the temporal and numerical components demanded opposite lever choices. According to the last-resort hypothesis, responding to the ambiguous probes should be based exclusively on total signal duration. By contrast, if rats are equally disposed to use either time or number as the basis for their responses (Meck & Church, 1983), lever choice is likely to be influenced equally by both components on an equal basis, irrespective of ambiguity.

I also examined whether inaccurate temporal cues would continue to influence choice behaviour in the presence of accurate numerical cues by using probe signals in which the number of events was fixed at two or eight while total duration was one of the intermediate values between 2.0 s and 8.0 s. This manipulation is based on Davis's (1993) contention that unless the environment is "sterilised" of competing nonnumerical cues, such cues will interfere with numerical discrimination. Cue accuracy was defined as the precision with which a signal represents one of the reinforced extreme signal attributes, with 4.0 s assumed to be a neutral cue. A final comparison of the interaction between time and number in controlling behaviour used probe signals where both time and number were totally concordant in the response demanded by each component (2e/2s; 8e/8s). The ambiguous, intermediate-time and concordant probe signals are collectively referred to as *preference probe signals*.

Given the results obtained, I did not progress with the complementary variation for number with duration fixed at 2.0 s or 8.0 s. However, to ascertain the relative control of the numerical and temporal components of the preference probe signals, a baseline reassessment was made by using the previous time and number probe signals.

Method

Animals and Apparatus

The animals and apparatus were the same as in Experiments 2.1 and 2.2.

Procedure

Training (Days 1-8 and 11). The rats were returned to the same procedure used in the first part of Experiment 2.2 for training with periodic time and number standards.

Baseline testing (Days 9 and 13). To provide a baseline against which to compare performance obtained during preference testing, the procedure was the same as used during periodic testing in Experiment 2.2.

Preference testing (Days 10 and 12). The procedure was the same as during baseline testing except that the probe signals were changed. For these preference probe signals, two sets of unreinforced signals were presented on 50% of the trials: a set of six periodic signals with the number of events held constant at 2 while total duration varied from 2.0, 3.0, 4.0, 5.0, 6.0, or 8.0 s (two-event preference probe); and a set of six test signals with the number of events held constant at 8 while total duration varied from 2.0, 3.0, 4.0, 5.0, 6.0, or 8.0 s (eight-event preference probe).

Data Analysis

To test the hypothesis that rats are equally likely to base lever choice on either temporal or numerical attributes of a compound signal, predicted performance was estimated by the following equation: Predicted $P(R|\ xe/ys) = (P(R|\ 4e/ys) + P(R|\ xe/4s))/2$, where $P(R|\ 4e/ys)$ and $P(R|\ xe/4s)$ are the performance for the corresponding time-relevant and number-relevant signals, respectively, obtained during baseline testing (Days 9 and 13). Performance measures did not differ across each pair of test days and were collapsed for the analysis presented here.

Results and Discussion

Experiment 2.4 produced some dramatic findings (see Figure 2.6). The first important aspect, however, was that the rats' ability to discriminate standard number-relevant signals was not disrupted by the novel conditions of preference testing. The obtained $P(R)$s for the two- and eight-event standards presented during preference testing (2e/4s and 8e/4s, Figure 2.6) were the

same or higher than that obtained during baseline testing, t(5) = 0.0 and t(5) = 2.2, respectively. By contrast, the rats appeared to have ignored number and responded entirely on the basis of time when accurate but conflicting temporal cues were also available. As Figure 2.6 shows, the obtained $P(R)$ for the two ambiguous preference signals, 2e/8s and 8e/2s, was the same as that for the corresponding time-relevant signals (4e/8s and 4e/2s), t(5) < 1.0; opposite to that obtained with the corresponding number-relevant signals (2e/4s and 8e/4s), t(5) > 11.3, and clearly different from predicted preference signal performance, t(5) > 9.5. These are exactly the results predicted by Davis and Memmott's (1983) last-resort hypothesis.

The data for concordant signals (2e/2s and 8e/8s), where both time and number are accurate cues for the same response choice, once more clearly showed that the rats' behaviour was not a compromise between the use of time and number. The obtained $P(R)$ was the same as

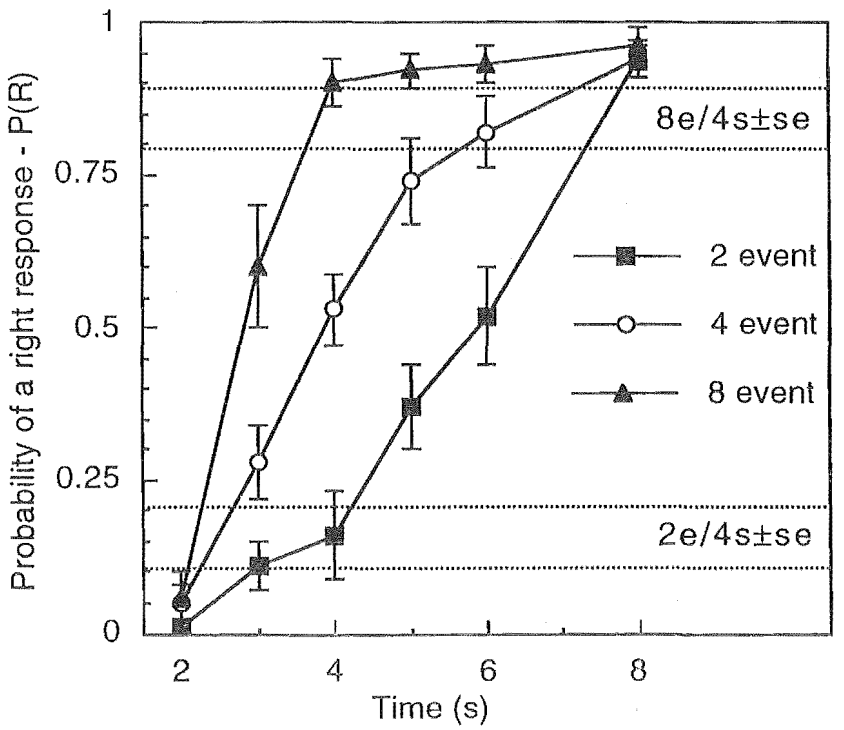


Figure 2.6. Mean probability of a right response (±SE) during testing in Experiment 2.4. Open circles show performance with time-relevant signals obtained during baseline testing. Filled squares show performance with the two-event preference signals and filled triangles with the eight-event preference signals obtained during preference testing. Also shown is performance obtained with the two- and eight-event standards during baseline testing (dotted lines). Predicted performance (P[R]; not shown) is midway between the appropriate number-relevant standard (2 or 8, dotted lines) and the appropriate time on the time-relevant curve (open circles; see text for details). 8e/4s = eight-event, 4-s; 2e/4s = two-event, 4-s.

for the corresponding time-relevant signals (4e/2s and 4e/8s), $t(5) < 1.26$, but significantly different to that obtained with the corresponding number-relevant signals, 2e/4s and 8e/4s, and predicted 8e/8s performance, $t(5) > 2.56$. The difference between the obtained 2e/2s $P(R)$ and the corresponding predicted performance failed to reach significance, $t(5) = 2.1$, $p = .09$.

The pattern of results for intermediate preference signals suggests that these signals can be divided into two groups. For the 2e/5s, 2e/6s, and 8e/3s signals, where the intermediate temporal component would be expected to encourage a response opposite to that demanded by the numerical component of the signal, the obtained $P(R)$s were similar to the predicted preference $P(R)$s and were all significantly different from their corresponding time-relevant and number-relevant $P(R)$s, $t(5) > 2.57$. For the second group of intermediate preference signals, the 2e/3s, 8e/5s, and 8e/6s signals, where the more probable response choice for the temporal dimension is concordant with the response demanded by number, the numerical and temporal components of the signal had, if anything, a combined effect on choice behaviour. With these signals, the rats were more likely to choose either the left or right lever than the probability indicated by either the corresponding predicted preference $P(R)$, time $P(R)$, or number $P(R)$, although only the comparisons between the obtained 8e/5s signal $P(R)$ and the corresponding predicted preference $P(R)$ and time-relevant $P(R)$ were statistically significant, $t(5) > 3.38$. In both groups of intermediate signals, the influence of temporal and numerical cues appears to be additive. When opposite response choices are indicated, performance appears to be a compromise between the two cues even though the numerical attribute of the signal provided the most accurate cue to guide choice behaviour. When the same response was indicated by the two signal attributes, performance always tended to be better than for either of the individual cues.

The most striking finding in Experiment 2.4 was that the numerical component of totally ambiguous signals appeared to have had absolutely no influence on performance, whereas the temporal component appeared to be in complete control of response choice. Even inaccurate temporal cues influenced choice behaviour in the presence of perfectly accurate numerical cues. These results occurred despite the rats having shown highly accurate numerical discrimination

when time was a neutral cue. The results support the view that complete control by number requires an environment that is sterilised of competing temporal cues (Davis, 1993).

General Discussion

Nonnumerical cues have been confounded with number in the periodic event sequences used by previous psychophysical studies of animals' numerical competence (e.g., Meck & Church, 1983; Roberts & Mitchell, 1994). The current use of unique signals is an important and novel modification of Meck and Church's (1983) original procedure because these signals minimise unwanted confounds with number. A remarkable demonstration of the rats' numerical competence was provided by the analysis of performance immediately after the sudden change to unique signals in Experiment 2.2. First, there was no decline in asymptotic performance across the change from periodic event sequences to unique sequences. Second, there was little systematic relationship between accurate numerical discrimination and deviation of either the temporal ratios or the patterns of the unique signals from the corresponding temporal ratio or pattern of the periodic signal. A similar level of performance was also attained by naive rats trained only with the unique signals in Experiment 2.3. Thus, the principal contribution of the present study has been to show rats can count events that occur at irregular intervals even when the temporal pattern of the sequence is unique at every presentation.

These results have important implications for the theoretical accounts of numerical discrimination by animals. Two main models of animal timing have been elaborated to explain the numerical discrimination of event sequences by animals. Meck and Church's (1983) mode-control model of timing and counting posits an "event mode" in which a relatively fixed number of pulses from a pacemaker is switched into an accumulator for each event so that the total quantity of pulses accumulated represents the numerosity of the sequence. The second model is a connectionist model of timing (Broadbent et al., 1993) which is based on a series of oscillators. It posits two alternative mechanisms for counting, based either on a temporal ratio or on a mechanism similar to the event mode. Broadbent et al. (1993) proposed that if a temporal ratio process represents numerosity, then regularly occurring events would be counted with

greater accuracy than events that occur at irregular intervals. The present data did not support this prediction, overall accuracy was the same for both regular and unique sequences (see Experiment 2.2).

The psychophysical parameters estimated here are similar for time and number and are consistent with those reported in previous studies using this range of values. The PSE approximated the geometric mean, and there was a position bias toward the 2e/2s lever. In addition, the slight increase in the DL and the Weber fraction in Experiment 2.2 provided some weak evidence that sensitivity to changes in numerosity was greater in the regular condition than in the unique condition. However, within the framework of the mode-control model, the switch must operate at least twice as often when processing numerical information compared with temporal information. Any increased variability in accumulation due to increased demands on the switching mechanism might be exacerbated when events occur at irregular intervals and lead to a lower sensitivity to number compared with time.

Taken together, the current findings suggest that an event mode or similar process is a more likely mechanism for counting in animals than a temporal ratio process. This is an important conclusion because an event mode (Meck & Church, 1983) meets a widely accepted formal definition of counting proposed by Gelman and Gallistel (1978; see also Broadbent et al, 1993; Church & Broadbent, 1990; Davis & Perussé, 1988; Gallistel, 1988, 1990; Thomas & Lorden, 1993).

The failure to replicate Meck and Church's (Experiment 1, 1983) earlier finding that time and number gained strong and equivalent control of choice behaviour after training with compound standards was surprising. That result was important because it suggested that rats readily learn about numerical cues in their environment, even in the presence of other competing cues. By contrast, the current use of an identical procedure revealed that although control by time was as expected from the earlier study, there was no evidence of control by number. Meck and Church (1983) provided no information on the experimental history of their rats, whereas the rats in Experiment 2.1 were experimentally naive, so this difference may underlie these conflicting findings. In the only other study similar to Experiment 2.1, Roberts and Mitchell (1994) claimed that their 6 pigeons produced results that "clearly replicate those of Meck and

Church's (1983)" (p. 68). In my view, Roberts and Mitchell (1994) also found much stronger control of choice behaviour by time than by number. In fact, the mean performance of their 6 pigeons was at chance for the eight-event probe signal: 8e/4s, $P(R)$ = 0.52 versus 4e/8s, $P(R)$=0.75. Only with the two-event probe signal was the pigeon's performance similar to performance with the corresponding time probe signal: 2e/4s, $P(R)$ = 0.24 versus 4e/2s, $P(R)$ = 0.20.

There is no obvious explanation as to why the current results conflict with those reported by Meck and Church (1983), but there is an explanation of Roberts and Mitchell's (1994) pigeon data that is consistent with the current findings. There are procedural differences between the rat and the pigeon studies that may account for the apparently discordant findings of Experiment 2.1 and of Roberts and Mitchell. Pigeons were tested for control by time and number across separate blocks of trials, and intermediate probe signals were reinforced, but most importantly, there was a fundamental difference in the temporal pattern of the event sequence presented to the pigeons. For the rats, event duration and interevent interval were equal and depended on the total sequence duration of the standard signal, but for the pigeons, the event durations were each fixed at 200 ms for every signal. This constraint on the pigeons' signals leads to a relatively large and potentially salient interval of 1800 ms between the second event and termination of the 2e/4s probe signal that approximates the total duration of the 2e/2s standard. Perhaps the pigeons responded on the basis of this 1800 ms duration when total sequence duration (4.0 s) did not provide a cue to guide choice behaviour, which would explain why performance on the 2e/4s signal was similar to that on the 4e/2s signal. The same terminal interval for the 8e/4s probe signal (300 ms) is quite unlike any temporal attribute of the training signals, except perhaps event duration, and I suggest that as a consequence response choice was at chance for this probe signal. Perhaps the psychophysical function for number obtained during testing in the pigeon study represented stimulus generalization based on a temporal attribute of the signal, the final interevent interval of the event sequence. Indeed, in a recent study using a delayed matching-to-sample version of Roberts and Mitchell's procedure, Roberts, Macuda, and Brodbeck (1995) argued that pigeons "used only the information at the end of . . . sequences" (p.185) to explain why they found a choose-long effect for time. This analysis is also consistent

with a marked bias shown by Roberts and Mitchell's pigeons toward the 2e/2s lever for number, compared with no obvious bias for time, that is otherwise difficult to explain. Thus, I suggest that the pigeons' behaviour in Roberts and Mitchell's study, like the current rats behaviour, was influenced by total duration rather than by number during training with the compound standards.

The natural utility of counting for animals is also a controversial issue (see Davis & Pérusse, 1988). Some researchers have suggested that counting is natural for animals (Meck & Church, 1983; Capaldi & Miller, 1988), whereas others have argued that counting has rarely been demonstrated outside the laboratory and has little natural utility for animals (Davis 1993; Davis & Bradford, 1986; Davis & Memmott, 1983; Davis & Pérusse, 1988; cf. Seibt, 1988). Although the data in Experiment 2.1 support the latter view, more impressive data in support of this viewpoint came from Experiment 2.4. In Experiment 2.4, rats that had already demonstrated excellent performance on both temporal and numerical discriminations after extensive training with separate time and number standards responded exclusively on the basis of time when novel signals presented both time and number as accurate but conflicting cues. In addition, inaccurate temporal cues continued to influence choice behaviour even in the presence of highly accurate numerical cues. These results are consistent with evidence that control by number was diminished in the presence of concomitant temporal cues in an autocontingency procedure (Davis & Memmott, 1983) and that both time and number influenced response choice in fixed-ratio schedules where time is a less accurate cue to reinforcement than number (Fetterman, 1993).

Cue salience is obviously important in the relative control of behaviour by time and number in psychophysical choice procedures and may be determined by many different factors such as discriminability, training contingencies, preexperimental experience, and species. Salience can be measured by rate of learning, and, when elements of a compound signal differ in salience, learning about the most salient element may overshadow learning about other elements of the stimulus (Kamin, 1969; Mackintosh, 1977). The failure of number, temporal ratio, or sequence pattern to gain strong control of choice behaviour in Experiment 2.1 is consistent with an overshadowing effect of the total duration of the compound time and number standards. Experiment 2.3 showed that naive rats acquired a temporal discrimination more rapidly than a

concurrent numerical discrimination, suggesting again that total duration is a more salient cue than number of events. Conversely, when temporal ratio and signal pattern were confounded with number in the regular event sequences used in Experiment 2.2, the change to unique signals did not disrupt performance. Experiment 2.2, then, indicated that the rats learned about the numerical cue but they did not appear to have learned about either temporal ratio or signal pattern even though both were also perfectly correlated with reinforcement. Thus, total duration appears to be more salient than number, but number seems to be more salient than temporal ratio or signal pattern. If this analysis is correct, then naive animals should learn a numerical discrimination more rapidly than a temporal ratio discrimination; and if they are trained with compound signals, where only number and temporal ratio are confounded, number should gain control of choice behaviour and temporal ratio should not.

The current evidence also suggests a modification to the mode-control model of timing and counting proposed by Meck and Church (1983). In this model, temporal and numerical information are processed in parallel into separate accumulators. This information is then transferred to working memory, and then both types of information are simultaneously compared with values stored in reference memory before a decision to respond is made (Meck & Church, 1983). The mode-control model was modified by Roberts and Mitchell (1994) so that temporal and numerical information have separate representations in working memory, but otherwise the decision stage continues to operate on both representations simultaneously. The current evidence is consistent with the idea that rats can simultaneously process temporal and numerical information, which may have separate working memory representations. However, I suggest that at the comparator stage this information is processed sequentially with the order of processing determined by salience. The most salient information is compared with reference memory values first, then comparisons are made to other available cue information in descending order of salience. The sequential comparator might be instantiated through associative strengths of cue information and would be a more efficient use of resources than parallel processing at this stage. This modification accounts for the overshadowing effect in Experiment 2.1 and for the stronger control of behaviour by time in experiments 2.1-4. Overshadowing occurs because only temporal information is processed first at the comparator stage so that numerical

information cannot become associated with reinforcement. Time has stronger overall control than number because the order of processing means that errors in processing temporal information can always influence the processing of numerical information but not vice versa. The modification is also consistent with the inverse hypothesis in which the strengthening of control by number is at the expense of control by time (Experiment 3, Roberts & Mitchell, 1994), a result that can be related to an acquired change in the order of processing at the comparator stage.

In summary, although numerical and temporal information can be processed simultaneously by rats during psychophysical choice experiments, total duration is a more salient cue than number. There appears to exist a natural bias toward the use of simple temporal cues, as these cues continue to influence rats' behaviour even in the presence of more accurate numerical cues. These findings support the last-resort hypothesis that rats count only in the absence of more salient cues (Davis & Memmott, 1983). Nonetheless, the second major contribution of the present study has been to provide the clearest demonstration to date of numerical discrimination by rats. This numerical discrimination does not appear to be an experimental artefact of temporal ratio discrimination or pattern recognition; rather, it is based on counting events.

Chapter 3

Timing and Counting by Rats: The Effects of Cerebellar Vermis and Hemisphere Lesions.

Section 1.6 summarised the recent evidence supporting a role for the cerebellum in temporal processing and showed that the exact nature of cerebellar involvement in timing is unclear (e.g., Clarke et al, 1996; Ivry & Keele, 1989; Nichelli et al, 1996; Perret et al, 1993). One prominent proposal, described here as the *millisecond timer hypothesis*, suggests that the cerebellum is a task-independent timing system with an influence restricted to the range relevant for motor timing, that is, up to about 1 or 2 s (Clarke et al, 1996; Ivry, 1996). According to this view cerebellar damage should disrupt timing in the milliseconds range but not in the seconds range. However, the analysis presented in Chapter 1 showed that the mode-control model of timing provides an alternative view which also makes a similar prediction. To account for the animal and human evidence that cerebellar damage usually produces deficits for interval timing in the millisecond range but not for durations outside this range (> 8 s; Clarke et al, 1996; Ivry & Keele, 1989; Kirk, 1985; Nichelli et al, 1996), it is proposed in the current thesis that damage to the cerebellum adds constant variability to the sensitivity of timing. As demonstrated in the formal analysis of timing (Section 1.4), any increase in the contribution of constant variability to timing would be more evident with brief intervals but its influence would be masked by scalar variability when timing longer durations. This proposal, referred to as the *constant variability hypothesis*, holds that the cerebellum is part of a distributed set of neural structures collectively responsible for timing over an extended temporal domain, from milliseconds to several minutes.

The following example provides a simple illustration of how the constant variability hypotheses accounts for the existing evidence on cerebellar damage and timing (for a formal

analysis, see Section 1.4.4). When timing a 200 ms interval it is reasonable to expect scalar variance in rats to be about 40 ms (ie. 20% of time) and constant variability to be about 20 ms. In this case, the proportion of constant variability to overall variability is 33%. However, for a 2 s interval, scalar variability increases to 400 ms, but constant variability remains at 20 ms and contributes only 5% to overall variability. Clearly, changes in constant variability would have a greater impact when timing 200 ms than 2 s. Thus, damage to brain regions that are involved with processes that contribute constant variability, such as the switch in the scalar timing model, might manifest itself as a deficit in interval timing performance at 200 ms but be masked by variability from other sources at 2 s. Considering the effects of cerebellar damage, this analysis provides a rationale for Nichelli's (1993) speculation that such neural damage adds variability to timing by adding random noise to switch latency.

The mode-control model also provides an account for numerical discrimination that can explain the similarity between the psychophysics of timing and counting in animals (Meck & Church, 1983; their Figure 1). The formal analysis of counting in Section 1.4.3 showed that variability attributable to the switch becomes proportional to number of events during counting because the switch operates at the onset of each event. If switch variance, for example, was equivalent to 20 ms and the pulses accumulated for each event were equivalent to 200 ms, the contribution of switch variability to overall variability (60 ms per event) would be 33%, irrespective of number of events counted. Thus, one intriguing consequence of the mode-control model is that a counting task provides a unique alternative for evaluating the nature of cerebellar involvement in timing. If the hypothesis is correct that damage to the cerebellum increases constant variability by contributing to increased switch variance, performance in a counting task should be disrupted by cerebellar lesions. This switch hypothesis is a specific form of the constant variability hypothesis because switch processes represent a major but not exclusive contribution to constant variability in timing. The constant variability hypothesis has greater generality because it is possible that there are other sources of constant variance in timing that do not have a major impact on variance in counting.

This counting prediction, as a specific form of the constant variability hypothesis, would not ensue from the millisecond timer hypothesis (Clarke et al, 1996; Ivry, 1996) unless

numerical discrimination involved millisecond timing. This possibility was resolved in Chapter 2 which showed that temporal cues associated with the periodic signals used in studies of animal counting do not form the basis for numerical discrimination. This finding is relevant to the current experiment because these temporal cues may have been within the range of the putative cerebellar millisecond timer. It was necessary also to establish, as was done in Chapter 2, that stimulus pattern did not form the basis of numerical discrimination because pattern recognition is another proposed cerebellar function (Braitenberg et al, 1997; Maill et al, 1993).

The trial unique signals developed in Chapter 2 obviate concerns that temporal or stimulus pattern cues associated with periodic signals might provide an alternative means of numerical discrimination following disruption to the counting process. The unique signals also have the advantage of potentially placing greater demands on the switch mechanism than periodic signals. In Experiment 2.3 it was suggested that with unique signals the higher Weber fraction for number compared with time may have been due to additional demands on the counting mechanism (i.e., the switch), a competition for attentional resources (Mackintosh, 1975; Roberts & Mitchell, 1994) or both. For example, when periodic signals are used in tests of numerical discrimination in animals the system could begin to anticipate events after the initial event and in this sense the switch might be primed. In fact, the duration of the first event provides this cue. Also, with periodic sequences, the interevent interval of the 8 event signal establishes a minimum latency between events (see figure 1.1). For these reasons the trial unique signals developed in Chapter 2 were used in the first part of Chapter 3.

Of added interest to the present study is the fact that a third view of the influence of cerebellar damage on timing was recently proposed by Gibbon et al (1997). This proposal, described here as the *scalar variability hypothesis*, was based primarily on a re-interpretation of Nichelli et al's (1996) psychophysical data, plus some preliminary findings by Malapani et al (1997, cited in Gibbon et al, 1997) that humans with cerebellar damage show deficits in temporal discrimination in the seconds range. Gibbon and his colleagues (Gibbon et al, 1997) suggested that the cerebellum contributes specifically to scalar variability in memory for

time, rather than to constant sources of variability or non-timing processes such as sustained attention (Nichelli et al., 1996, see Section 1.6.3). Any disruption to sources of scalar variability should produce impairments irrespective of the time range used, because scalar variability is proportional to subjective time. Their view is similar to the constant variability hypothesis only in that both consider the cerebellum to be part of a set of structures responsible for timing processes across an extended temporal domain. If Gibbon et al (1997) are correct, then rats with cerebellar lesions should be impaired in a similar way across both millisecond and seconds time ranges. In contrast, the constant variability hypothesis predicts that the effects of cerebellar lesions on interval timing should depend on the time range involved, with performance impaired in the millisecond range but not the seconds range. Both the scalar variability and the constant variability hypotheses, in its the switch form, predict impairments in numerical discrimination after cerebellar damage, though for different reasons. However, only according to the former hypothesis should the disruption of counting be accompanied by a similar disruption in seconds range timing.

Experiment 3.1

The comparative role of different cerebellar regions in timing performance is largely unknown but some human work suggests that it is only the lateral cerebellum that is critical to interval timing (Ivry et al, 1988). However, there is some direct evidence that the fastigial nucleus, the major output of the cerebellar vermis, can modulate DA levels in the CPu and SN in complementary manner (Section 1.6). In addition, a recent anterograde tracing study has shown that there is some modest convergence of cerebellar and basal ganglia projections on the ventral medial nucleus and parafascicular nucleus (Denaiu et al, 1996). These convergent fields provide a possible basis for both lateral and medial cerebellar modulation of basal ganglia function that may include interval timing processes (Meck, 1996). For these reasons, Experiment 3.1 compared the effects of lesions to either the cerebellar vermis or hemispheres on timing and counting by rats. Part 1 of the present chapter examined the effects of these

lesions on rats' ability to discriminate both the number of events (2 - 8) and total duration of an event sequence (2 - 8 s) using a psychophysical choice procedure that employed the trial-unique timing and numerical signals developed in Chapter 2. In Part 2, the rats were trained and tested in a millisecond range task (200 - 800 ms).

Method

Animals and Apparatus

The animals and operant chambers were the same as in Experiment 2.3. The photocell activity cages were constructed of clear Perspex (30 x 40 x 18 cm high), with a wire mesh lid, and fresh sawdust scattered on the floor for each animal. Activity was recorded using two photoelectric beams, 8 cm from each end of the longer wall and 1 cm above the floor. The testing room was dimly lit with two 22-W fluorescent lamps.

Surgery and histology.

Surgery was performed under clean conditions using aseptic materials and the animals received an oral antibiotic (Tetravet; Oxytetracycline HCL) for 3 days after surgery. Anaesthesia was induced with Ketamine (65 mg/kg ip.) and Xylazine (5 mg/kg ip.) in equal volumes of physiological saline. In addition, 0.2 ml/kg of Vasolamin 5% (50 mg/ml sc., Tranexamic acid) was administered prior to surgery as an aid to clotting. Rats were randomly allocated to 3 matched groups prior to surgery, based on the parameters obtained through the curve fitting procedure described in Experiment 2.1. Eleven rats received aspiration lesions of the cerebellar vermis (VERM). The skull was trephined 2 mm posterior to lambda and 2 mm both sides of the midline, extending posteriorly to and along the external occipital crest. This section of skull was removed and the exposed vermal cortex and underlying white matter aspirated with the aid of a dissection microscope. Eleven rats received bilateral aspiration lesions of the cerebellar hemispheres (HEM). These lesions were produced by trephining the interparietal bone, bilaterally, approximately 3 mm lateral to the midline, from 2 mm posterior

of lambda to the occipital ridge and laterally to the external suture. Both sections of bone were removed and the exposed hemispheric cortex and underlying white matter was aspirated. These lesions were intended to remove as much as possible of the cerebellar vermis and hemispheres while sparing the underlying nuclear complex. The cavities created by the lesions were loosely packed with saline moistened gelfoam. Ten rats received sham lesions (SHAM) that included all surgical steps of either the VERM or HEM groups except aspiration of any cerebellar tissue.

At the conclusion of the study the rats were overdosed with sodium pentobarbital and perfused intracardially with physiological saline followed by 4% formalin. The brains were removed and stored in formalin for at least 3 days before being blocked and embedded in wax. Fifty micron sections were taken of the entire cerebellum and every third section stained with cresyl violet. The lesions were reconstructed by tracing the outline of each lesion onto an image of the appropriate section of a control brain with the aid of Adobe Photoshop©. The relative number of pixels contained within this outline provided an estimate of lesion extent.

Procedure

Part 1: 2 - 8 s timing and counting

Pre-surgery training (Days 1 to 52). Pre-training and training with unique signals was as described in Experiment 2.3.

Pre-surgery bisection testing (Days 53 to 55). The testing procedure with unique signals was also as described in Experiment 2.3.

Post-surgery activity testing (Day 62): Activity in a photocell cage was measured immediately prior to the first post-surgery test session as a general measure of the influence of cerebellar lesions on behaviour. The number of individual beam interruptions (breaks) and the number of these breaks that occurred consecutively for both beams (crossings) was recorded in 10 min. bins during a 50 min. session.

Post-surgery bisection testing (Days 63 to 65 & 72 to 74): These two blocks of testing were identical to pre-surgery testing and were separated by 6 days of training.

Post-surgery training. (Days 66 to 71): This training was identical to pre-surgery training.

Part 2: Millisecond timing

Training (Days 1 to 35). Training was identical to that in Part 1 except that the rats were only presented with 2 time-relevant white-noise signals presented pseudo-randomly, with a left lever response reinforced when signal duration was 200 ms and a right lever response reinforced when total duration was 800 ms. This training commenced about 3 months after surgery.

Bisection Testing (Days 36 to 38). The conditions of training were maintained except the two training durations were presented on 50% of the trials. On the remaining trials five unreinforced test signals, with durations of 300, 400, 500, 600 and 700 ms, were presented pseudo-randomly and with equal probability.

Data Analysis

The data analysis was the same as that for the experiments in Chapter 2. Responses with latencies greater than 3.0 s were excluded in any figures or calculations. Training data are reported as percentage correct, and test data are reported as proportion of responses on the right lever (P[R]). As previously, p(A), gave an estimate of overall performance; p(R|~A), a measure of position bias; the point of subjective equality (PSE), the difference limen (DL) and Weber fraction (DL/PSE) provided bias free estimates of performance during testing (Figure 1.1; for details see Experiment 2.1). Mean values are reported plus or minus the standard error of the means.

The data from millisecond training in Part 2 were transformed to A' to provide a bias free measure for estimation of rate of acquisition and asymptotic performance using a function

based on the linear operator model (Bush & Mosteller, 1955). The parameters obtained for asymptotic performance showed the same pattern as percentage correct over the last 6 days of training, so following the convention adopted for training data in Part 1, percentage correct is reported.

Seven rats failed to acquire the numerical discrimination successfully and are not included in any analysis for Part 1. However, because these rats could successfully perform the temporal discrimination, they were given surgery and subjected to the same experimental conditions as the remaining rats so that they could be used as subjects in Part 2 (2 SHAM, 3 VERM, 2 HEM). After surgery, 2 rats died (1 HEM, 1 VERM) and 3 rats (2 SHAM, 1 HEM) consistently had greater than 15% of long latency responses (> 3 s, all other things being equal, this was usually a sign that something was wrong with the rat or the equipment). As a consequence, the number of rats in each group that performed in both the timing and counting tasks for part 1 was reduced so that for the SHAM group, n =6, the VERM group, n = 7 and the HEM group, n = 7. The loss of 5 animals postoperatively meant that the mean group data from bisection testing prior to surgery were no longer identical (although there were no significant group differences). To minimise the potential influence of any pre-surgery scores, post-surgery test measures were analyzed with 2-way Ancova's using the corresponding pre-surgery parameter measure as a covariate.

There was also a concern that because events within each signal could vary in duration from 100 ms to over 1 s, any deficits found in timing or counting could be due to impairments related to processing short duration stimuli. For example, short duration events in a sequence might have been missed as the result of attentional deficits. If this was the case, the mean first event duration should be lower for signals followed by an incorrect lever choice compared with signals followed by a correct lever choice and a similar situation would exist for the mean duration of all events comprising a signal. For these reasons, the duration of the first event in a signal and the mean duration of all events comprising a signal (mean event duration) was calculated for every signal presented in all postoperative training sessions (not enough data were available for analysis during test sessions). The mean first event duration and the mean mean event durations were also calculated separately for signals followed by an

incorrect choice and a correct choice for each rat across post-surgery training sessions and these data were analyzed by 3-way Anova.

In Part 2, all rats were re-trained because all the surviving rats had been subject to the same experimental conditions throughout Part 1. Only one rat had a consistently high percentage of long latency responses during re-training and, as a consequence, the number of subjects in each group for Part 2 were: SHAM group, n =9; VERM group, n = 10 and HEM group, n = 10.

Results

Motor effects and activity testing

The rats in the VERM group, with the exception of 1 rat, showed obvious signs of ataxia and tremor immediately after surgery but all recovered rapidly (in 3 to 6 days) before the activity testing commenced. There were no overt signs of motor impairment in the HEM group and this is consistent with the observation that clear motor deficits are generally absent after lesions to the lateral cerebellum (Houk & Barto, 1996). With respect to photocell activity, two-way (Group X Bins) Anova's revealed that the pattern of results were comparable for both breaks and crossings so only the latter is presented in detail (Figure 3.1). There was a main effect of group $F(2, 19) = 9.14$, $p < 0.002$, with overall activity comparable for both lesions groups but significantly less than the overall activity for the SHAM group ($p < 0.002$, HEM; $p < 0.02$, VERM; Neuman-Keuls). There was also a main effect of Bins ($F(4, 76) = 50.20$, $p < 0.0001$) reflecting habituation but this was similar for all groups (Group X Bin, $F(8, 76) = 1.63$).

Part 1: Seconds timing and counting

The data from initial training and the pre-surgery test session were reported in Chapter 2 (Experiment 2.3) so only a summary of these data are provided here. Prior to surgery, rate of

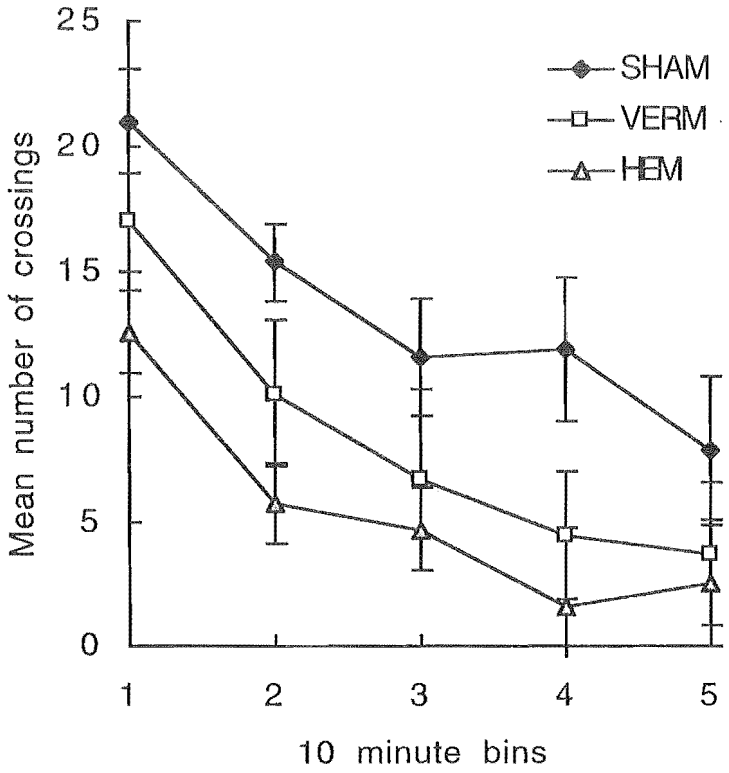


Figure 3.1. Activity testing in Part 1: Mean (±SEM) number of consecutive beam interruptions (crossings) across each 50 min session during. SHAM = sham operated group; VERM = cerebellar vermis lesioned group; HEM = cerebellar hemisphere lesioned group.

acquisition and asymptotic performance was significantly better for time across all three groups. The psychophysical bisection tests confirmed the superior overall performance on time compared with number and that the rats' sensitivity to changes in time was greater than sensitivity to changes in number (Mean Weber fraction, 0.20 ± 0.02 and 0.30 ± 0.03, respectively), whereas the PSE was the same for both time and number (at the geometric mean of the extremes, i.e., 4).

In terms of overall percentage correct during training sessions, performance on both discriminations post-surgery was unchanged from pre-surgery levels and was comparable across the three groups (Post-surgery group effects, $F[2, 17] = 2.96$ for time, and $F[2,17] < 1.0$ for number). Mean percentage correct for the 6 training days before surgery compared to the 6 training days after surgery was as follows: for time, 97% ± 1.0 vs 97% ± 0.4, for group SHAM; 93% ± 2.6 vs 96% ± 0.9, for group VERM; and 92% ± 2.6 vs 95% ± 0.5, for group HEM. For number, 92% ± 1.6 vs 92% ± 1.2, for group SHAM; 88% ±

2.4 vs 89% ± 1.7, group VERM; and 84% ± 2.3 vs 85% ± 2.7, for group HEM. The mean percentage of training trials excluded under the 3 s latency criterion post-surgery was similar for all groups: 2% ± 0.8 and 2% ± 1.1, for group SHAM, 3% ± 1.1 and 3% ± 1.0, for group VERM, 3% ± 0.9 and 2% ± 0.5, for group HEM, for time and number respectively.

Although there were no differences between the groups in overall performance during post-surgery training, the relationship between errors and event durations was still examined for the reasons given in Data Analysis. For each signal length (2 or 8), a Group (SHAM vs VERM vs HEM) x Signal (Time vs Number) x Choice (Correct vs Incorrect) ANOVA on the data revealed a significant main effect of signal, $F(2, 20) > 1000$, $p < 0.01$, as expected because signal type (time or number) as well as signal length constrains event duration. However, there were no significant main effects of group, $F(2, 20) < 2.2$, $p > 0.14$ and no significant Group x Signal, $F(2, 20) < 4.5$, $p > 0.11$ or, more importantly, Group x Choice, $F(1, 20) < 1.91$, $p > 0.18$ interactions. There was a significant Signal x Choice interaction, $F(1, 20) = 4.45$, $p < 0.05$, for the mean first event duration in 2 event and 2 s signals. The mean first event durations for 2 s signals were similar irrespective of choice, 201 ± 1 ms for a correct choice (short) and 198 ± 6 ms for the wrong choice (long), $F(1, 3) < 1$, whereas mean first event durations of 2 event signals were significantly shorter for a correct choice (few) compared to the wrong choice (many), 940 ± 6 ms and 1006 ± 28 ms, respectively, $F(1, 3) = 5.11$, $p < 0.04$. Otherwise there were no other significant or near significant main effects, 2-way or 3 - way interactions.

Mean performance during bisection testing in Part 1 is shown in Figure 3.2. During post-surgery bisection testing, for both time and number, the mean percentage of trials excluded under the 3 s latency criterion was the same or less than those excluded during pre-surgery testing for all groups. The variance explained by the curve fitting procedure was high for all groups across both timing and counting for all sessions (> 96%), except for counting in the first post-surgery test (92%± 3, SHAM; 88% ± 5, VERM; and 78%± 9, HEM) for which there was no significant group difference, $F(2, 18) = 1.5$. Figure 3.3 shows the group parameters estimated during pre-surgery and post-surgery bisection testing for time (left

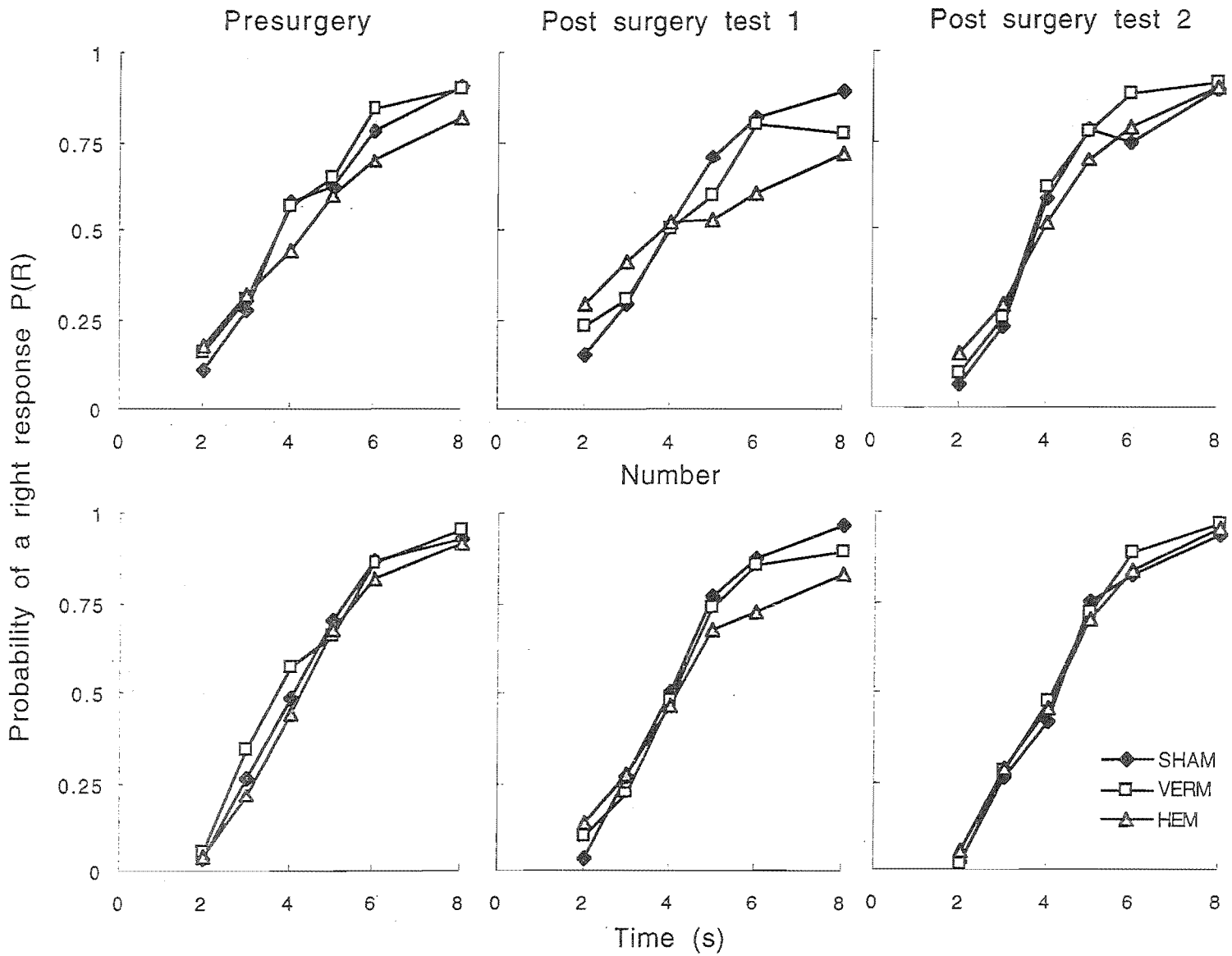


Figure 3.2. Mean probability of a long response (±SE) as a function of time (top panels) and number (bottom panels) for pre-surgery bisection tests (left panels), first post-surgery bisection test (middle panels) and second post-surgery bisection test. SHAM = sham lesioned group, VERM = cerebellar vermis lesioned group and HEM = cerebellar hemisphere lesioned group.

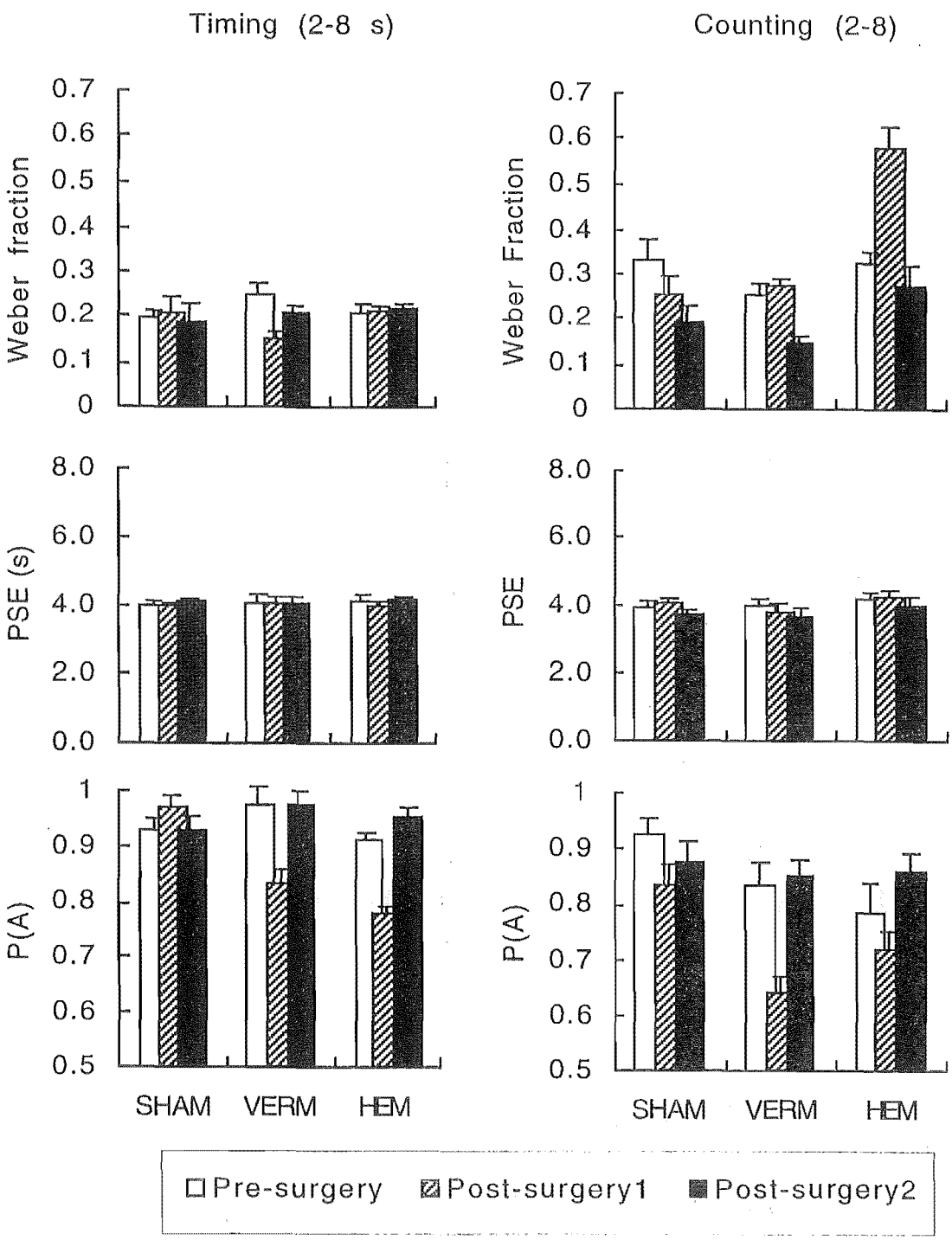


Figure 3.3. Mean (±SEM) Weber fractions (top panels), PSEs (middle panels) and p(A)s (bottom panels) for time (left) and number (right) obtained during pre- and post-surgery testing in Part 1. SHAM = sham operated group; VERM = cerebellar vermis lesioned group; HEM = cerebellar hemisphere lesioned group.

panels) and number (right panels). The pattern of results for DL was similar to that for Weber fraction and for this reason only the latter is shown in Figure 3.3.

There were no differences between groups in the pre-surgery bisection test for time (across 2 - 8s) for any of the estimated parameters ($F(1,17) < 2.19$, $p > .14$; Figure 3.3, left panels). Post-surgery, two-way (Group x Session) Ancova's also showed no Group, Session or Group x Session effects for PSE, DL or Weber fraction, $F(2,16) > .71$, $p > .41$. Although p(A) dropped for the VERM and HEM groups in the first test session following surgery and recovered completely by the second post-surgery test session, the Group x Session interaction failed to reach significance, $F(2, 16) = 6.63$, $p > .07$; the main effect of session for this measure was significant, $F(1, 16) = 6.63$, $p < .02$, but there was no main effect of Group, $F(2,16) = 1.24$, $p > .32$. The PSEs for the time discrimination post-surgery were highly stable at the geometric mean of the extremes for all groups (ie at 4s), as were the pre-surgery PSEs.

For number, the PSEs, DLs, and Weber fractions were comparable across groups during pre-surgery bisection testing ($F[1,17] < 1.81$, $p > .19$; Figure 3.3, right panels). The p(A) for number during pre-surgery testing was higher for the SHAM group and lowest for the HEM group, but these differences were not significant, $F(1, 17) = 2.75$, $p > .09$. After surgery, the only clear group differences that emerged for number were in terms of the Weber fraction (Figure 3.3, top right panel). The Ancova for post-surgery Weber fractions confirmed a significant group main effect, $F(2,16) = 3.80$, $p < .05$, due to the HEM group having a higher mean Weber fraction than the other groups (Neuman-Keuls, $p < .05$ relative to group SHAM, and $p < .06$ relative to group VERM; see Figure 3.2). The DL scores also suggested sensitivity differences between groups ($F(2,16) = 3.19$, $p < .06$); again, group HEM showed poorer sensitivity (DL = 1.58 ± 0.33 s) than either group SHAM (DL = 0.87 ± 0.13 s) or group VERM (DL = 0.70 ± 0.11 s). As with time, the PSEs for number post-surgery were the same as pre-surgery values, did not differ across groups post-surgery ($F(2,16) < 1.0$, $p > .9$) and were approximately at the geometric mean of the extremes. The p(A)s were also the same for all groups post-surgery, $F(2, 16) < 1.85$,

$p > .19$. There were no significant Group x Session interactions post-surgery for any of the parameters estimated for number, $F(2,16) > 1.26$, $p > .30$. There were, however, significant session main effects for p(A), DL, and Weber fraction ($F(1, 16) > 5.69$, $p < .03$), but not for PSE, $F(1, 16) < 1.0$, $p > .96$.

Part 2: Millisecond timing.

All rats, including those that failed to acquire the number discrimination in Part 1 of the experiment, successfully acquired the millisecond discrimination (Figure 3.4). The curves fitted to the A' measure (a bias-free measure of overall performance) for each rat showed that the rate of acquisition estimate was the same for all groups; 0.16 ± 0.04, SHAM; 0.15 ± 0.02, VERM; 0.15 ± 0.02, HEM; $F(2,26) < 1.0$, $p > .9$, but that there was a significant

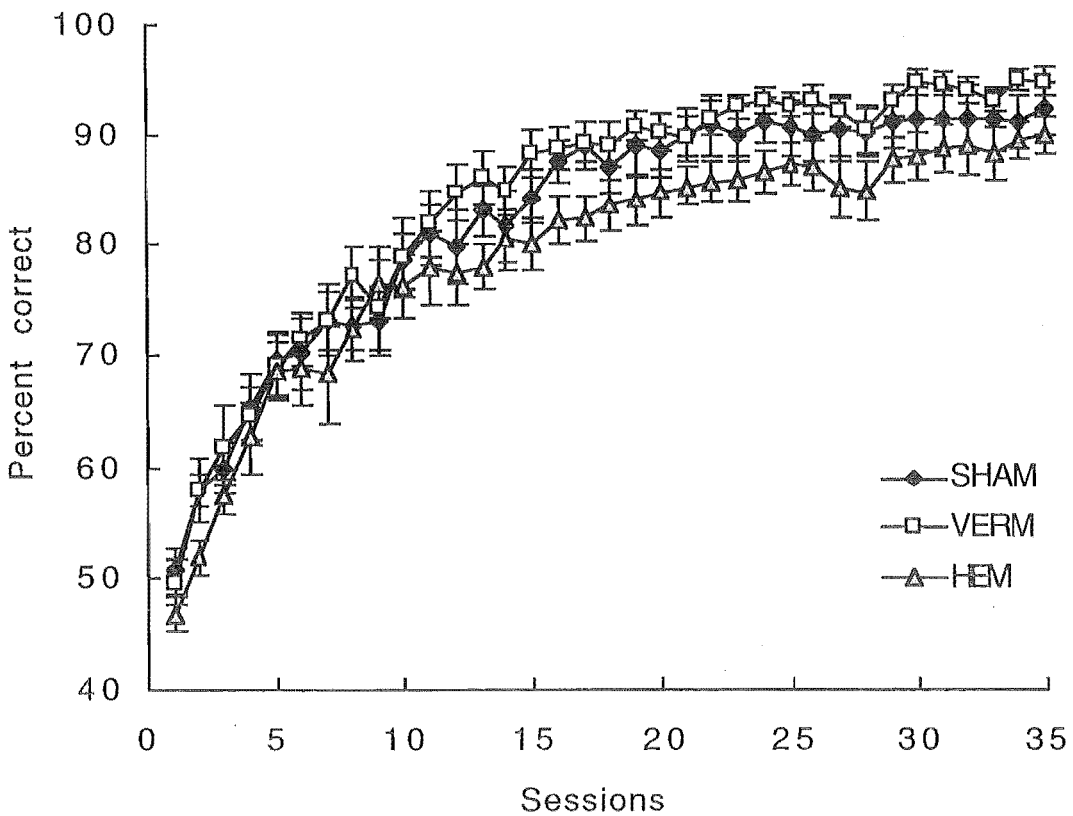


Figure 3.4. Mean (±SEM) percentage correct during training of lesioned and sham rats on the millisecond bisection task in Part 2. SHAM = sham operated group; VERM = cerebellar vermis lesioned group; HEM = cerebellar hemisphere lesioned group.

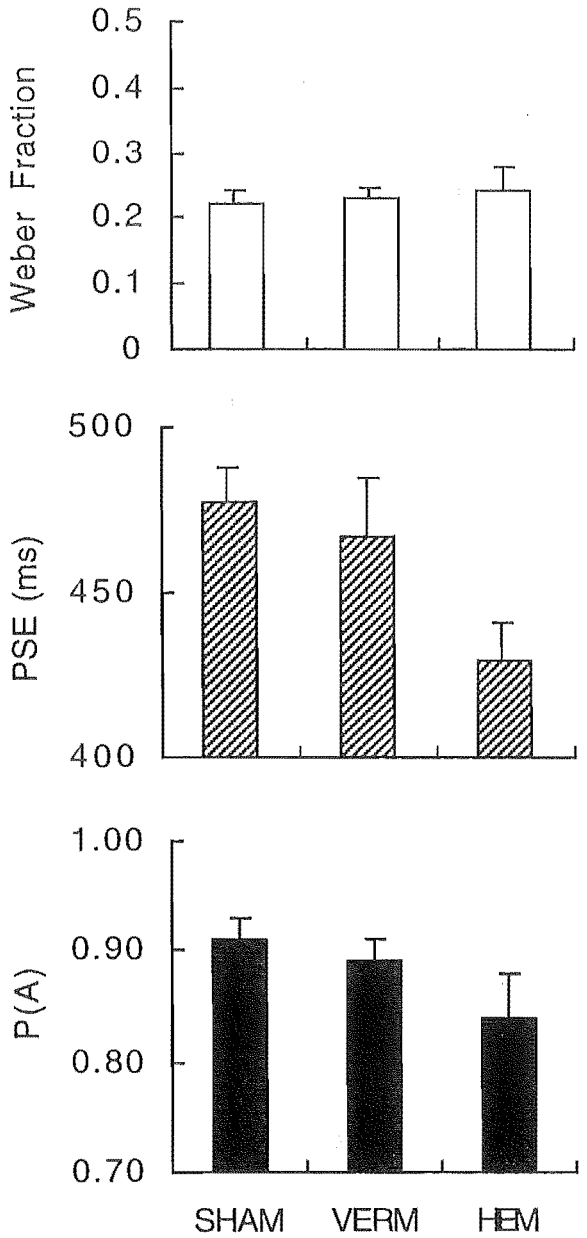


Figure 3.5. Mean (±SEM) Weber fractions (top panels), PSEs (middle panels) and p(A)s (bottom panels) obtained during millisecond testing in Part 2. SHAM = sham operated group; VERM = cerebellar vermis lesioned group; HEM = cerebellar hemisphere lesioned group.

difference in the estimate of asymptotic performance; 0.95 ± 0.01, SHAM; 0.95 ± 0.01, VERM; 0.89 ± 0.02, HEM; $F(2, 26) = 3.86$, $p < .04$. An analysis of the mean percentage correct over the last 6 days of training confirmed the difference in asymptotic performance between the groups, $F(2, 26) = 4.14$, $p < .03$. Neuman-Keuls showed the HEM group (89% ± 0.02) attained asymptotic performance that was significantly lower than both the SHAM

group (94% ± 0.02) and the VERM group (94% ± 0.01; p's < 0.04; note the similarity between these mean percentage correct and the estimated A' asymptotic performance for each group).

The difference in percentage correct between groups found during training was not maintained during bisection testing, primarily because of an increase in variability by the HEM group. Overall performance, as estimated by p(A), decreased during testing for all groups (0.91 ± 0.02, SHAM; 0.89 ± 0.02; VERM and 0.84 ± 0.04; HEM) and there was no significant difference, $F(2, 26) = 1.97$, $p > .16$ (Figure 3.5, bottom panel). The rats sensitivity to changes in millisecond duration was similar across groups, there was no difference in either DL or Weber fraction, $F(2, 26) < 1$ (Weber fraction, see Figure 3.5, 2; mean DL = 106 ± 1 ms for SHAM group; mean DL = 108 ± 15 ms for VERM group; and mean DL = 103 ± 14 ms for the HEM group). By contrast, the PSE was significantly different between groups, $F(2, 26) = 3.76$, $p < 0.04$ (Figure 3.5). The mean PSE for the HEM group was significantly lower (Neuman-Keuls, $p < 0.05$) than the corresponding PSE of both the SHAM and VERM groups (Figure 3.5).

Histology.

Figure 3.7 shows reconstructions of the smallest and largest lesions. The lesions of the cerebellar vermis destroyed almost all of lobules 6, 7 & 8 (mean 97%, 95% & 85%, respectively). All vermis rats showed some damage to lobule 9 and the vermal region of lobules 2 & 3 (mean 26% and 22%, respectively). Lobules 10 and 1 remained intact although there was slight damage to the fastigial nucleus in 2 vermis rats (mean 2.3%). The vermis lesion seldom encroached into the hemispheres (Crus 1 and 2, the paramedian lobule and copula pyramis, mean < 5%; Simplex lobule, mean 8%).

In the cerebellar hemisphere lesions, Crus 1 and Crus 2 were almost completely destroyed (mean 97%) and most of the paramedian and simplex lobules were destroyed (means 70% and 85%, respectively). There was also some damage to the lateral portions of lobule 6 (mean 26%), lobules 4 and 5 (mean 18%) and lobule 7 (14%). Damage to other

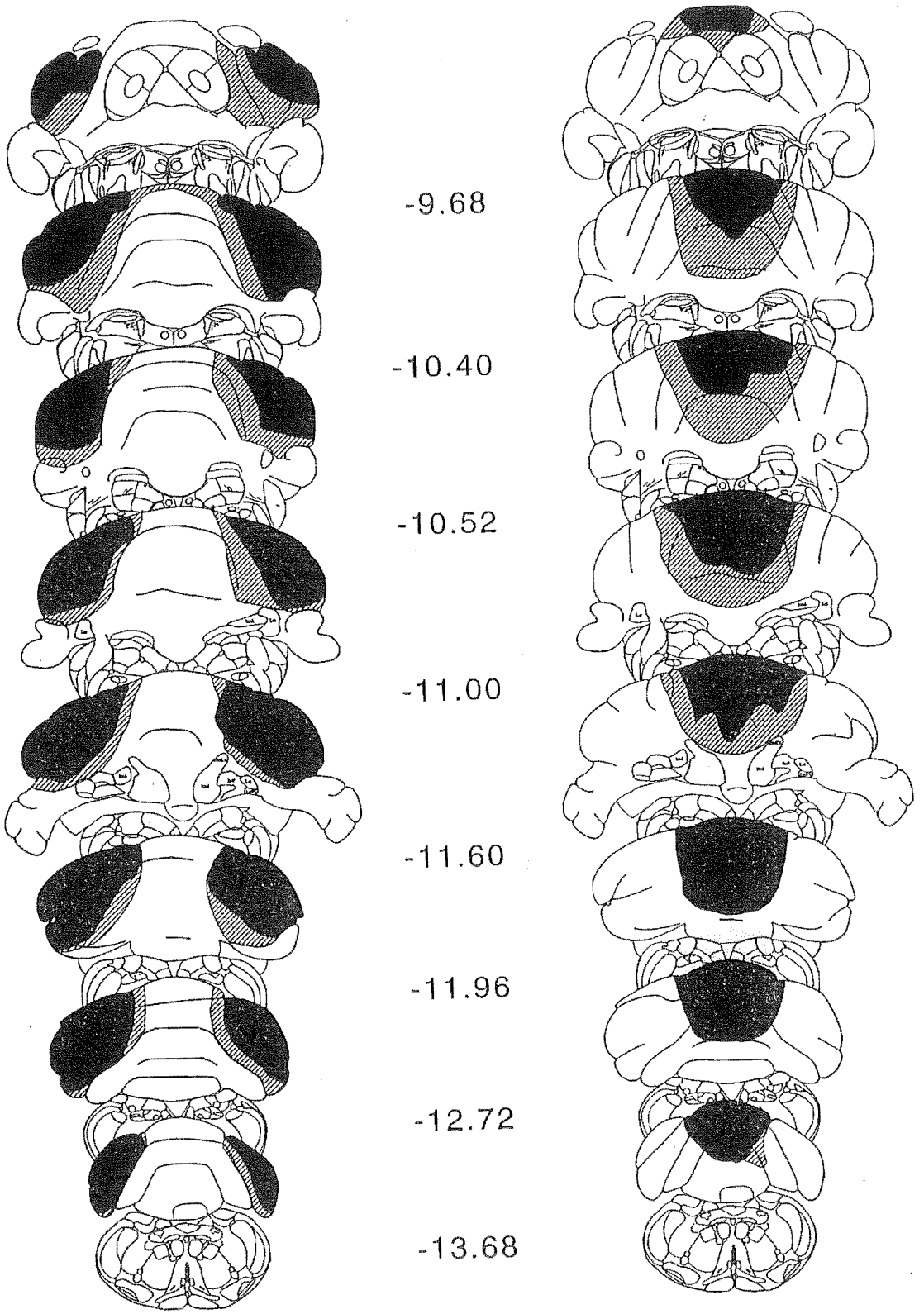


Figure 3.5. Reconstructions of the smallest (solid) and largest (hatched) cerebellar hemisphere (left) and vermis (right) lesions. Coronal sections are adapted from Paxinos and Watson (1986) and coordinates are mm posterior to bregma.

regions of the cortex was very slight (mean < 9%) and there was slight damage to cells in the dorsal region of the dentate-interpositus nuclei complex in most hemisphere rats (mean 3.6%).

Discussion

Studies with animals and humans have implicated the cerebellum in interval timing, but its precise influence on these processes remains unclear. In the present experiment, rats with lesions to the cerebellar hemispheres showed poorer overall performance in acquisition of a millisecond discrimination and had a lower PSE during bisection testing in this task compared with vermis lesioned and sham operated rats. The hemisphere group's sensitivity to a numerical discrimination, as defined by the Weber fraction, was also poorer than the vermis and sham groups, whereas sensitivity to a concurrent temporal discrimination in the seconds range revealed that the latter was not disrupted by cerebellar hemisphere lesions.

Two alternative suggestions have previously been made regarding the possible influence of the cerebellum on perceptual timing. The scalar variability hypothesis suggests that the cerebellum is a source of scalar variability (i.e., variability which is proportional to the interval being timed) in a distributed system that is involved in timing over a range that extends from milliseconds to minutes and possibly hours (Gibbon et al, 1997). According to this view cerebellar damage should disrupt timing in both the millisecond and seconds ranges. The second proposal, the millisecond timer hypothesis, is that the cerebellum operates as a task independent timing system that is restricted to the millisecond range (< 1 to 2 s, Clarke et al, 1996; Ivry, 1993; Ivry & Keele, 1989). This second view holds that cerebellar damage should disrupt timing in the millisecond range only. A third alternative, the constant variability hypothesis, was examined in this chapter. This hypothesis acknowledges that the cerebellum is involved in timing processes that operate over an extended time range but contends that it contributes constant rather than scalar variability to timing. This latter view proposes that cerebellar damage should disrupt milliseconds range timing but leave seconds range timing relatively unimpaired; as explained in the Introduction, it has also generated the

novel prediction that counting should be affected by cerebellar lesions. The pattern of results described in Chapter 3 is consistent with the hypothesis that damage to the neocerebellum adds constant variability to timing precision through its role in the neural processes that subserve both numerical discrimination and timing over an extended temporal domain.

In clear contradiction of the predictions made by the scalar variability hypothesis, there was no evidence that cerebellar hemisphere lesions disrupted sensitivity for temporal discrimination in the 2 - 8 s range. Although both cerebellar lesion groups showed a temporary disruption in overall performance (p[A]) for 2 - 8 s timing for the first post-surgery test session in Part 1, this measure of timing performance is independent of measures of sensitivity such as the difference limen and Weber fraction (Blough, 1996). Sensitivity to time in Part 1 was the same for cerebellar hemisphere, vermis, and sham groups and was extremely stable across pre-surgery and both post-surgery test sessions. These findings are consistent with previous animal studies that report no apparent deficits in temporal discrimination following lateral cerebellar lesions for durations > 15s (Clarke et al, 1996; Kirk, 1985).

Clarke et al's (1996) initial experiment showed that, like the current study, performance was the same or improved for lesioned and control groups across pre-surgery and post-surgery conditions in the seconds range. Estimates based on their mean data showed Weber fractions of 0.17 in both pre-surgery and post-surgery testing for the cerebellar rats (Weber fractions calculated from the PSE and standard deviation (SD) that were reported, given that Weber fraction = SD*0.675/PSE). For Clarke et al's (1996) consistency score measure (which would appear to confound Weber fraction and p[A]) there was a significant interaction between the milliseconds and seconds range. Their cerebellar rats became more consistent in the seconds range while becoming less consistent in the millisecond range. In contrast to this animal work, Nichelli et al (1996) found impaired sensitivity to time in cerebellar patients' performance on an 8 -32 s bisection task, although their data were poorly fitted by the psychophysical functions compared to the control data. As indicated earlier (Section 1.6.3), these human data may have been related to the increased attentional demands of a concurrent suppression task that their subjects performed during the bisection task and perhaps also the

reported attentional difficulties shown by cerebellar patients (Akshoomoff & Courchesne, 1994, 1992; see also Ferrara, Lejeune & Wearden, 1997).

The slight but significant impairment in asymptotic performance shown by hemisphere rats during discrimination training in the milliseconds range (Part 2) suggests that cerebellar damage leads to disruption of performance which is only present on some trials only. The reader is reminded that inattention (1-p[A]) represents discrimination that is not based on the temporal attributes of a signal whatever the reason (Church et al, 1976). It may be possible that disruption to a millisecond timer or additional noise at the switch (the constant variability hypothesis) contributes to this inattention although this is difficult to reconcile in either case without evidence of increased variability. Bisection testing showed that hemisphere rats' had shorter PSEs than vermis and sham rats but there was no direct evidence of impaired sensitivity to millisecond durations as measured by either the difference limen or the Weber fraction. Interestingly, Clarke et al (1996) also found a shift in their bias score measure for cerebellar rats that was similar to the change in PSE found in the current study, although this result was not replicated in their second experiment. However, Clarke et al's bias score confounds position bias (simply called bias in this thesis) with response bias (i.e., PSE), and thus their reported shift towards the short lever could be the result of a change in either measure or a combination of both.

Although both the millisecond timer and constant variability hypotheses imply that sensitivity should have been impaired over and above changes in PSE during bisection testing, this null result is not entirely unexpected in rats that were trained postoperatively and had relatively long-standing lesions. Nichelli et al (1996) found shorter PSEs but the same sensitivity to time as control subjects when cerebellar patients were tested using an analogous bisection procedure with a millisecond time range (100-900 ms). This is the same result as the current findings with hemisphere lesioned rats that, like the cerebellar patients, had existing cerebellar lesions before training and testing in a comparable time range (200-800 ms). The cerebellar patients did show poorer sensitivity than control subjects but equivalent PSEs in the 100-600 ms task and then no deficits in the final task (100-325 ms). However, as suggested in Section 1.6.3, it is possible that the pattern of results shown by cerebellar

patients was related to an impaired ability to adjust sensitivity in timing to changes in conditions (i.e., the reduced ratio between the extremes) or for sensitivity in timing to benefit from practice. More importantly, it is suggested that with enough training both human and non-human subjects with cerebellar damage can reach the level of sensitivity in timing shown by intact subjects and the type of timing deficit may depend on the amount of training and other procedural factors.

Clarke et al (1996) reported that although hemisphere lesioned rats showed impaired sensitivity immediately after surgery there was evidence of functional recovery with continued training, possibly due to a reorganization within intact regions of the cerebellum. A similar kind of functional recovery following the extensive training that the current hemisphere rats received prior to testing in Part 2 may have influenced their performance during the millisecond bisection tests, resulting in a lower PSE rather than decreased sensitivity to time. However, given the large lesions to the lateral cerebellar cortex in the current study and the view that the cerebellum is part of an extended timing system, an alternative basis for recovery of function seems more likely; other intact brain regions that subserve this timing system may be able to compensate for deficits related to cerebellar damage. For example, forebrain dopaminergic systems might play a modulatory role in interval timing such as gain control by adjusting the signal to noise ratio (see Figure 4 in Cohen & Servan-Schreiber, 1992). If damage to the cerebellum adds a constant source of noise to the timing system, it is possible that subsequent changes in dopaminergic tone might result in an increase in gain or responsiveness of neurons elsewhere in the timing system, resulting in some recovery of interval timing performance in the millisecond range. Alternatively, the cerebellum may be more directly involved in controlling signal to noise ratios, for example, in reducing constant noise as a consequence of practice or in relation to particular task demands.

The subtle effects of cerebellar hemisphere lesions on millisecond timing performance by both rats and humans offers, at best, only weak support for the millisecond timer hypothesis. If the cerebellar hemispheres provided an independent central millisecond timing mechanism that was critical to interval timing performance, it would be reasonable to expect a large and sustained disruption to millisecond timing performance, particularly after the large

hemisphere lesions the rats in the current study sustained. In the seconds range, for example, the substantial nigra and caudate putamen are hypothesized to provide a neural basis for the clock processes involved in timing. Neurotoxic lesions to these brain regions appear to severely disrupt all aspects of timing performance which does not appear to be ameliorated by further training (Meck, in press, cited in Meck, 1996).

In contrast to the millisecond timer hypothesis, the constant variability hypothesis can accommodate subtle deficits in timing performance following damage to the lateral cerebellum because the cerebellum is viewed as a non-critical part of an extended network of neural structures that subserve interval timing. As alluded to above, this extended interval timing network may be able to compensate for damage to some of its constituent parts, such as the cerebellum, in ways that are dependent on both recovery and training so that the specific nature of the deficits may vary according to these and other (e.g., lesion) factors.

Cerebellar hemisphere rats in Part 1 showed a lower sensitivity to numerosity (the numerical discrimination) compared to the vermis and sham lesion rats that, in combination with the unimpaired sensitivity in 2-8 s range timing, can be accounted for only by a specific form of the constant variability hypothesis that proposes cerebellar lesions add noise to switch processes in the mode-control model of timing and counting. There were no differences in overall counting performance (p[A]) between the groups after surgery. Although performance dropped for the vermis group in the first post-surgery bisection test, it was the same as prior to surgery for all groups in the second post-surgery bisection test. In the first post-surgery bisection test, however, the discrimination of intermediate values by some rats in the cerebellar hemisphere group was disrupted to the extent that the data were relatively poorly fitted by the psychometric function whereas (non-significantly) better fits were obtained for the vermis and sham groups. By the second post-surgery test session, the data from all groups were equally well fitted by the predicted function yet the hemisphere group still showed a higher difference limen and Weber fraction, indicating a lower sensitivity to changes in numerosity, than the vermis and sham groups. Interestingly, for the vermis and sham groups there was unexpected improvement in sensitivity to number in the second post-surgery test session relative to pre-surgery performance, to levels similar to those found for

the temporal discrimination. While there was no obvious reason for this improvement, these results suggest a reduction in switch variability in the vermis and sham rats. A reduction of memory/comparator variability (the major source of scalar variance in timing) is an unlikely basis for the improvement in sensitivity because this should have resulted in a decrease in the difference limens and Weber fractions for the concurrent 2-8 s discrimination also. The effects on sensitivity to number found in post-surgery test 2 are reminiscent of Nichelli et al's (1996) millisecond timing data in that it was primarily an improvement in controls that appeared to underpin their cerebellar effects on sensitivity to time.

It is unlikely that the current numerical discrimination findings are confounded by any impairment of non-numerical processes. First, Chapter 2 showed that numerical discrimination of event sequences is not correlated with temporal characteristics of the sequence, such as the ratio of event duration to total duration or sequence pattern, that covary with number. This is an important consideration because deficits in numerical discrimination might otherwise have been related to impaired millisecond or seconds range timing or impaired pattern recognition mediated by the cerebellum. The use of trial unique event sequences obviates these concerns. A related concern was that cerebellar lesions might disrupt the processing of short duration stimuli per se. The analysis comparing the duration of events in signals associated with errors with those associated with correct responses indicated that errors are not related to the brevity of events that comprise the signal. The only significant difference, between event duration and lever choice, showed that the duration of the first event tended to be longer when errors where made following the 2 event/ 4 s signal. Across groups there was no evidence that rats made more errors when the duration of the first event in a sequence or the mean duration of all events comprising the sequence was particularly short in either timing or counting. This finding is consistent with previous results from rats and humans that also suggest that the processing of non-temporal attributes of short duration stimuli (e.g., frequency or intensity) is not impaired by cerebellar damage (Clarke et al, 1996; Ivry & Keele, 1989). Finally, although the current hemisphere rats showed reduced levels of general activity in an open field immediately prior to post-surgery testing, this is unlikely to have influenced numerical discrimination. Vermis rats showed the same reduction

in general activity yet their sensitivity to number was the same as sham rats and clearly better than the hemisphere rats. The percentage of response latencies greater than the 3 s criterion, which can also be considered a measure of general activity, was also the same for all groups during all bisection tests.

Although the vermis lesioned rats showed a similar reduction in overall activity to hemisphere lesioned rats postoperatively, their performance throughout the study was not significantly different to sham operated animals on any other measure of performance. For vermis rats, p(A) dropped in the first post-surgery test for both time and number but had recovered completely by the second post-surgery test. More importantly, the vermis lesioned rats' Weber fraction was either the same or better than pre-surgery levels in both post-surgery tests for both time and number. In millisecond range training and testing (Part 2) all aspects of performance were similar to the sham group. These findings that cerebellar vermis lesions did not impair millisecond or seconds range timing supports Ivry et al's (1988) contention that only the lateral cerebellum is involved in timing processes.

To conclude, I reiterate the fact that the experimental evidence for cerebellar lesion effects on temporal discrimination is still scant (Clarke et al, 1996; Gibbon et al, 1997). The lack of any effects of cerebellar lesions on seconds range timing in the current work runs contrary to the prediction of Gibbon et al (1997) that cerebellar damage contributes increased scalar variance to timing. It is also reasonable to expect marked deficits in millisecond timing after cerebellar hemisphere lesions if Ivry (1993, 1997) is correct in describing this structure as an important, independent timing system limited to the millisecond range. On the contrary, the evidence provided here and elsewhere in the literature (e.g., Clarke et al, 1997) suggests that disruption of millisecond timing is quite subtle; in the present study these subtle effects occurred despite the loss of up to 90% of the lateral cerebellar cortex. The subtle millisecond timing deficits, together with the more robust evidence that cerebellar hemisphere lesions impair discrimination of number described here, offer support for the view that cerebellar hemisphere damage contributes constant variability to a general and neuroanatomically distributed timing mechanism responsible for an extended temporal domain.

Chapter 4

Millisecond and Seconds Range Timing in Rats: The Effects of Lesions to the Cerebellar Hemispheres and Nucleus Accumbens.

The findings of Experiment 3.1 suggested that the cerebellar hemispheres may be involved in the switch processes associated with timing and counting. The results showed that rats with lesions to the cerebellar hemispheres had higher Weber fractions for number than rats with cerebellar vermis or sham lesions, whereas the Weber fractions for seconds range timing were similar for all experimental groups. Cerebellar hemisphere involvement in millisecond timing was suggested by the poorer overall performance in acquisition of a millisecond range discrimination by hemisphere rats compared with vermis and sham lesioned rats. These findings offer support for the constant variability hypothesis which proposes that cerebellar damage adds constant variance to interval timing in a distributed timing system described by the mode-control model. The counting deficits are not easily explained by the millisecond timer hypothesis and the absence of any evidence of disruption to seconds range timing was inconsistent with the scalar variability hypothesis (Gibbon et al, 1997).

Contrary to expectations, the estimated Weber fractions obtained during millisecond testing in Part 2 of Experiment 3.1 were similar for all groups, although hemisphere rats had a significantly lower PSE than either vermis or sham lesioned rats. It was suggested that the neural systems which subserve temporal discrimination are able to compensate for the deficits produced by damage to cerebellar hemispheres and the extensive postoperative training that hemisphere rats received prior to millisecond testing may have facilitated this. Thus, the effects of cerebellar damage on the sensitivity of millisecond timing may have

been masked by increased efficiency in other parts of the timing system. For example, in Part 2 of Experiment 3, a reduction in scalar variability and increased memory speed, similar to that found with vasopressin and oxytocin (see Meck, 1983), could account for the lower PSE found in the hemisphere lesioned rats. In this event, the Weber fraction for hemisphere rats would have been similar to the Weber fraction for the vermis and sham groups because a compensatory reduction in scalar variability may have masked increased constant variability in the hemisphere rats. These speculations are also consistent with Clarke et al's (1996) finding of an increase in their [response + position] bias measure, towards the short lever, and the decrease in their consistency measure for millisecond range timing combined with an increase in this consistency measure for seconds range timing.

Experiment 4.1

The purpose of Experiment 4 was to examine the effects of cerebellar hemisphere lesions on millisecond and seconds range interval timing, in rats that had been trained on these discrimination tasks prior to surgery. Although there were no differences between groups in the rate of acquisition of the millisecond discrimination in Part 2 of Experiment 3, the lower asymptotic performance found in hemisphere rats may still reflect some form of deficit related to learning the temporal discrimination rather than disruption of timing processes per se. The absence of any deficits in millisecond sensitivity and the lower PSE found in hemisphere lesioned rats must be viewed in light of the relatively long-standing lesions and extensive training the rats received before the millisecond bisection testing. The results in Part 2 of Experiment 3.1 may also have been influenced by the fact that cerebellar lesions could have a differential effect on temporal discriminations acquired postoperatively compared with those acquired preoperatively. For example, Kirk (1985) found that vermis lesions following preoperative training did not produce deficits on the a DRL schedule, whereas DRL performance acquired after lesions was severely disrupted (although probably unrelated to disrupted timing, see Section 1.6.2).

As stated earlier, the only other study to examine the influence of the cerebellar hemispheres[1] on performance in both millisecond and seconds range timing, found that there was an initial impairment in millisecond timing only and that even this effect recovered relatively rapidly (Clarke et al, 1996). In contrast to Part 2 of Experiment 3.1, Clarke et al's rats were trained preoperatively on both timing tasks and the only statistical tests performed were on their own global measures of performance, consistency score and bias score. Their consistency score, however, appears to confound DL and p(A) which are assumed to be independent indicators of discrimination performance (Blough, 1996). In addition, control rats were not included in any statistical tests because of the small sample size (n = 3). More evidence of cerebellar involvement is obviously needed and it is important to replicate Clarke et al's (1996) findings with more standard measures, such as DL and Weber fraction, that do not confound sensitivity to time with overall performance (estimated by p[A]).

Neurotoxic lesions to the nucleus accumbens (NAC) were chosen as the comparative lesion because the mesolimbic and nigrostriatal dopamine systems play an important role in seconds range timing (Meck, 1988). For example, acute administration of the dopaminergic agonist haloperidol, which has strong affinity to D_2 receptors in both the mesolimbic and mesostriatal dopaminergic systems, decreases pacemaker rate and increases Weber fraction in the seconds range for rats (Maricq & Church, 1983) and disrupts sensitivity to time in humans (Rammsayer, 1993, 1997). Rammsayer has suggested that the roles of mesostriatal and mesolimbic dopamine systems in temporal discrimination are dissociated, with the former involved in millisecond timing and the latter involved in seconds range timing (Rammsayer, 1997).

In the present study, the NAC was chosen over lesion sites in the nigrostriatal system because of concerns that lesions to the SN or CPu might prove too disruptive, particularly to motor activity, whereas rats with lesions to the NAC show no obvious motor impairments (Wishaw and Kornelsen, 1993). These latter concerns over the impact of

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[1] Through bilateral lesions to the dentate nucleus, the primary output for the lateral cerebellar cortex.

nigro-striatal lesions appear to have been borne out in a recent study by Meck (in press, cited in Meck, 1996) where SN and CPu lesions severely disrupted seconds range timing, although this report suggests that the NAC itself may not be directly involved in timing.

If the suggested dissociations exist between neural systems involved in millisecond and seconds range timing, cerebellar hemisphere lesions should disrupt millisecond timing but leave seconds timing unaffected (Ivry and Keele, 1989; Keele & Ivry, 1987; Ivry et al, 1988; Keele and Ivry, 1990) whereas disruption of the mesolimbic system may have the inverse effects (Rammsayer, 1997). Given the arguments developed in the current thesis supporting a single distributed timing system that is responsible for temporal information processing in both time ranges, and that cerebellar damage adds constant noise to this system (Chapter 3), the following alternative is possible: cerebellar lesions should disrupt millisecond range timing only, whereas mesolimbic lesions may disrupt timing in both time ranges. Part 1 of the current experiment tested these predictions by examining the effects of bilateral lesions to the cerebellar hemispheres or NAC in rats trained preoperatively on both 200 to 800 ms and 2 s to 8 s bisection tasks.

The findings of Chapter 3 and the transient nature of the deficits described by Clarke et al (1996) suggest that the lasting effects of cerebellar lesions might be quite subtle. This may be because the cerebellum plays a non-critical role in interval timing or because the timing system compensates for deficits associated with cerebellar damage. As suggested in Chapter 3, reductions in constant noise from other parts of the timing system might compensate for increased constant noise associated with cerebellar damage. Alternatively, and depending on the relative contribution of constant and scalar variability to overall variability in a particular time range, a reduction in scalar variance might also compensate for an increase in constant variance leaving the level of total variance relatively unchanged. In either case, subtle deficits in timing performance might be more easily detected by testing the animals over a series of different time ranges. Only one previous parametric study has examined temporal discrimination in rats for durations less than 1 s (Church et al, 1976). Their data suggest that there is a sharp increase in constant variability between 500 and 1000 ms (Figure 1.3A, left panel). However, the nature of temporal discrimination in rats

for durations less than a second is relatively unknown. For these reasons, the rats from Part 1 of Experiment 4 were trained and tested on 2 additional bisection tasks within the assumed range of Ivry's millisecond timer, 100 to 400 ms and 300 to 1200 ms, and on 2 other bisection tasks, 1 s to 4 s, and 3 s to 12 s, the latter being within the range normally used in the work on scalar timing (Gibbon et al, 1984).

Testing across several time ranges provides an additional test of one of the 3 competing hypotheses for the role of the cerebellum in timing. The constant variability hypothesis, like the millisecond timer hypothesis, predicts disruption of millisecond range timing but also entertains the possibility of compensatory effects across time ranges because it views the cerebellum as part of an extended timing system responsible for temporal processing from milliseconds to much longer durations. Thus, increased constant variance may trigger compensatory reductions in scalar variability. The overall outcome may be the paradoxical effect that an initial increase in overall variability in the millisecond range should return to postoperative levels accompanied by a relative reduction in overall variability in the seconds range. It was also intended that this range of durations may provide the parameters for a preliminary attempt to estimate the level of scalar and constant variability with the generalised Weber function (Equations 1.2 or Equations 1.15c and 1.16 with the Poisson constants, a_I and $\underline{B}$, respectively, set to zero).

Method

Animals and Apparatus

The subjects were 36 experimentally naive female Wistar rats (*Rattus norvegicus*), about 1 year old at the start of training. Housing, test conditions, and apparatus were the same as those used in Experiments 3.1 except that two additional operant boxes, identical to Boxes 5 and 6, were added, giving a total of 12 boxes.

Surgery

Surgical procedures were the same as in Experiment 3.1. The rats were randomly allocated to 3 matched groups prior to surgery on the basis of the parameters obtained in the first bisection tests. Twelve rats received lesions to the NAC (NAC, n = 12) through bilateral infusions of 1 µl/2 min 0.09 M NMDA (Sigma Chemicals) via a 30-gauge micro-syringe with a further 2 min allowed for diffusion before the syringe was retracted and the skin sutured. The 90 nmol NMDA solution was obtained by dissolving 13.24 mg in 1 ml phosphate buffer (pH 7.4) and the final pH was adjusted to 7.4 with 2 M NaOH solution. The coordinates were obtained from the atlas of Paxinos and Watson (1986, incisor bar 2.3 mm below the inter-aural line): AP, + 1.6 mm from bregma; ML ± 1.7 mm; DV - 6.8 mm (from dura). Twelve rats received bilateral aspiration lesions of the cerebellar hemispheres (HEM) in the manner described in Experiment 3.1. Ten rats received sham lesions (SHAM), that involved either injection of the saline vehicle used for the NAC group, n = 5, or all the surgical steps for the HEM group except the aspiration of any tissue, n = 5.

At the conclusion of behavioural testing, the rats were overdosed with sodium pentobarbital and perfused intracardially with physiological saline followed by 4% formalin. The brains were removed and stored in formalin. Prior to sectioning, the cerebellums were blocked and embedded in albumin-gelatine. Frozen sections (50 µm) were taken through the entire extent of the lesions for all brains and every third section was mounted and stained with cresyl violet. The lesions were reconstructed as described in Chapter 2.

Procedure

Part 1: 200 - 800 ms and 2 - 8 s timing

Pretraining. Pretraining was the same as in Experiment 2.1.

Pre-surgery training (Days 1-60). The animals were trained with two sound durations of either 200 ms and 800 ms (the millisecond range) or 2 s and 8 s (the seconds range) on alternate days. For each rat, the sound for one duration range was white noise and for the other duration range it was a 2000 Hz tone, and the same lever either left or right was designated the "long" lever for both duration ranges. The type of sound, the lever designated "long," and the time range presented on a particular day, were counterbalanced across animals. On each trial the rats were presented with a sound duration and both levers were inserted at the termination of the sound signal. The rats were reinforced for pressing the *short* lever following a 200 ms duration or a 2 s duration. A response on the *long* lever was reinforced following a 800 ms duration or a 8 s duration. On each trial one of the two signals from the appropriate range was presented randomly with a probability of 0.5. If the rat made the correct response, condensed milk was delivered immediately; if the rat made an incorrect response no reinforcer was delivered. Both levers were retracted when either lever was pressed or after an interval of 8 s with no response. Intertrial intervals (ITIs) were 5 s plus a randomly distributed duration with a mean of 35 s (range 1 s to 69.9 s). During the first five days of training a signal that was followed by an incorrect response was repeated on the next trial (correction procedure). Sessions were conducted daily and lasted 3 hrs. The type of response and its latency was recorded for each trial.

Pre-surgery bisection testing (Days 61 to 64). The conditions of training were maintained (i.e., millisecond and seconds range testing on alternate days) except that one of the two training signals was presented with a probability of 0.25 on each trial. On the remaining trials one of four unreinforced test signals was presented with equal probability.

For the millisecond range test days, the test signals were 300 ms, 400 ms, 500 ms, and 600 ms in duration and on the seconds range test days the test signals were 3 s, 4 s, 5 s, and 6 s in duration.

Post-surgery bisection testing (Days 84 to 87 & 114 to 117). These two blocks of testing (post-surgery test 1, Days 84 to 87, and post-surgery test 2, Days 114 to 117) were identical to pre-surgery and were separated by 26 days of training.

Post-surgery training (Days 88 to 113). This training was identical to pre-surgery training.

Part 2: 100 to 400 ms, 300 to 1200 ms, 1 to 4 s and 3 to 12 s bisection tasks.

Training (1 to 14 and 19 to 32). Training was the same as in part 1 with the following differences. The rats were randomly divided into 2 groups and assigned a millisecond and seconds range discrimination task. One group of rats was trained with either 100 ms (short lever) and 400 ms (long lever) or 1 s (short lever) and 4 s (long lever) on alternate days, and then following bisection testing, trained with either 300 ms (short lever) and 1200 ms (long lever) or 3 s (short lever) and 12 s (long lever) on alternate days. The order of training was the reverse for the second group. Training lasted 14 days for all rats and recommenced immediately after the first block of bisection testing. The correction procedure was used for the first 2 days of both blocks of training.

Bisection testing (Days 15 to 18 and 33 to 36). The testing procedure was identical to Part 1 except that the rats were tested for a total of 4 days alternating between a millisecond and a seconds condition depending on the pre-test training the rats received. For each time range condition the unreinforced test signals were, 150, 200, 250, 300 and 350 ms (100 - 400 ms condition), 450, 600, 750, 900 and 1050 ms (300 - 1200 ms condition), 1.5, 2, 2.5, 3 and 3.5 s (1 - 4 s condition) and 4.5, 6, 7.5, 9 and 10.5 s (300 - 1200 s condition).

Data Analysis

The method of estimating rate of acquisition and asymptotic performance during preoperative training is described in Data Analysis for Experiment 3 and the method used to estimate psychophysical parameters from the mean test data (Equation 2.1) is described in the Data Analysis for Experiment 2.1.

There was, however, a strong tendency in post-surgery test 1 for the non-linear estimation procedure to fit Equation 2.1 as a step function rather than an ogive, whenever overall performance was poor, resulting in unrealistic estimates of the standard deviation (i.e., approaching zero, for 2 of the HEM rats and 5 of the NAC rats). In addition, there was a significant correlation between estimated P(A) and the Weber fraction thus calculated for the seconds range, $r = 0.49$, $p < 0.01$. This significant association is a violation of the assumed independence between sensitivity and overall performance underlying Equation 2.1. In contrast, there was no correlation between these two parameters for the pre-surgery test or post-surgery test 2 nor any tendency to fit step functions on those occasions. It should also be emphasised that there was no correlation between p(A) and Weber fraction nor any tendency to fit step functions in Experiment 3.1, particularly for the first post-surgery test session in Part 1 of that experiment, even in the HEM group which showed the most disrupted performance on that occasion. Although variance explained was also lower for the HEM group compared to the other experimental groups in the first bisection test in Experiment 3.1, these differences were not significant. By contrast, some significant differences in variance explained by Equation 2.1 arose in the first postoperative test session of the current experiment (see Results below).

For these reasons, statistical tests comparing performance in post-surgery test 1 with preoperative test performance in Experiment 4 were based on parameters estimated by a linear estimation method (PSE, DL and Weber fraction) and using Heinemann et al's (1969) computational formulae (p[A] and bias). Although the non-linear method using Equation 2.1 will generally produce more accurate parameter estimates because it takes all data points into account and is preferred, the older computational method and the linear regression

method should still produce reasonable estimates when the conditions preclude the use of non-linear methods. For the pre-surgery bisection testing and the first post-surgery bisection test parameters for each rat were re-estimated in the following way. Estimates of $p(A)$ and $p(R|\sim A)$, position bias (see Data Analysis, Experiment 2.1), were obtained using the equations,

$$p(A) = p(L|L) - p(L|S), \tag{4.1}$$

and,

$$p(R|\sim A) = p(L|S)/(1 - p[A]), \tag{4.2}$$

where $p(L|S)$ is the probability of a long response given the short standard and $p(L|L)$ is the probability of a long response given the long standard (Heinemann et al, 1969, Heinemann & Chase, 1970). Estimates of the PSE, DL and the Weber fractions were obtained by fitting a straight line ($ax + b$) by the method least squares to the proportion long responses associated with each of 5 sets of 3 adjacent signal durations. The PSE, DL and Weber fraction were calculated from the straight line with the greatest slope (PSE = $[0.5\text{-}b]/a$), DL = $([0.75 - b]/a - [0.25 - b]/a)/2$; Maricq & Church, 1983; see also Maricq et al, 1981; Meck et al, 1984). A comparison between the estimates obtained by the computational formulae and the linear regression method and those obtained through non-linear estimation (Equation 2.1) for preoperative testing is presented in the Results.

One rat became ill during pre-surgery training and was dropped from the study, 2 hemisphere lesioned rats died after surgery and 3 rats had a consistently high percentage of response latencies > 3 s. As a consequence, the number of rats in Part 1 was reduced so that for the SHAM group, n = 9, the NAC group, n = 11 and the HEM group, n = 10. Another sham rat died towards the end of experiment, and is excluded from any analysis in Part 2. Due to a malfunction in box 11 on the last day of Part 2 testing the data for 3 subjects on this day were not included in any analysis.

Results

Part 1: Preoperative performance in 200 - 800 ms and 2 - 8 s timing.

Rate of acquisition and asymptotic performance during pre-surgery training was more rapid for the seconds range bisection task compared with the millisecond range bisection task (Figure 4.1A). The curves fitted to the A' measure for individual rats (see Part 2, Experiment 3) showed that both rate of acquisition and asymptotic performance was significantly better for the seconds range discrimination compared with the millisecond range discrimination; mean rate of acquisition, 0.55 ± 0.05 and 0.23 ± 0.02, for seconds and milliseconds, respectively, $t(29) = 6.54$, $p < 0.01$; mean asymptotic performance, 0.98 ± 0.00 and 0.97 ± 0.00, for seconds and milliseconds, respectively, $t(29) = 2.41$, $p < 0.01$.

For the pre-surgery bisection test, parameters estimated by non-linear estimation showed the following. Although overall performance was extremely accurate in both time ranges, it was higher in the seconds range (mean p[A] = 0.93 ± 0.01) than in the millisecond range (mean p[A] = 0.91 ± 0.01, $t[29] = 2.29$, $p < 0.03$). The psychophysical functions for 200 to 800 ms and 2 to 8 s did not superpose when plotted in relative real time (Figure 4.1B) but approached superposition when plotted in relative subjective time, although systematic deviations from superposition are evident at the extremes (Figure 4.1C). The mean PSE for the seconds range was below the geometric of the extremes (4 s, PSE = 3.70 ± 0.08 s, rather than 4 s) whereas the mean PSE for the millisecond range was above the geometric mean of the extremes (PSE = 425 ± 79 ms, rather than 400 ms). The mean Weber fraction for seconds range timing was significantly lower than the mean Weber fraction for millisecond range timing (0.17 ± 0.01 versus 0.23 ± 0.01, respectively, $t[29] = 4.28$, $p < 0.01$), as predicted by the generalised Weber function. The mean position bias towards the short lever was similar for both time ranges, 0.13 ± 0.04 and 0.15 ± 0.04 for seconds and millisecond conditions, respectively, and the mean variance explained was identical (98 ± 0%).

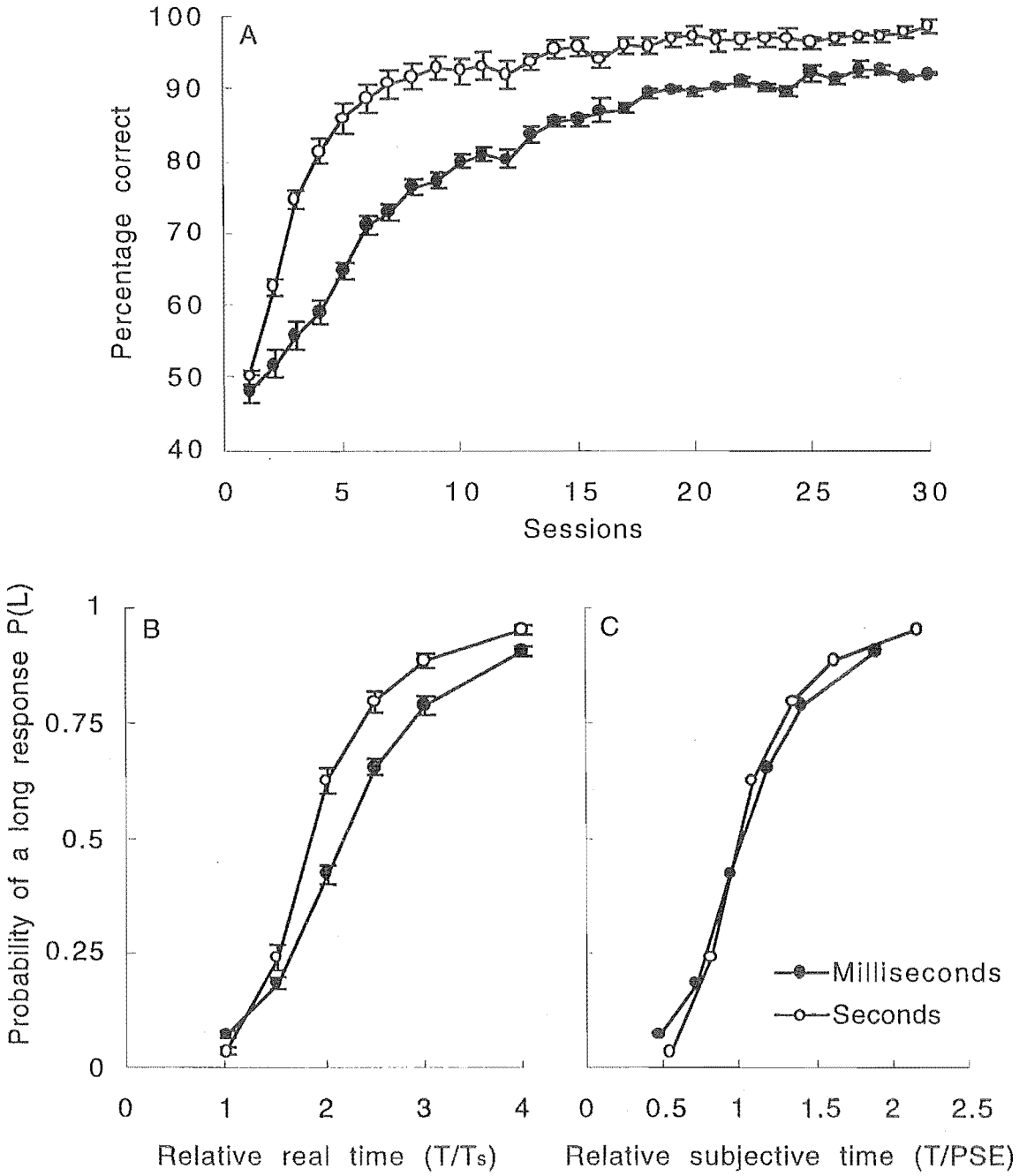

Figure 4.1. Panel A: Percentage correct (±SE) as a function of training sessions in Part 1 for millisecond range signals (200 ms and 800 ms) and seconds range signals (2 s and 8s). Panel B: Mean probability of a long response (±SE) as a function of relative real time (time divided by the short standard). Panel C: Mean probability of a long response as a function of relative subjective time (time divided by the PSE).

Analyses of the preoperative test data were also made using Hienemann et al's (1969) equations and the linear regression method to compare with those obtained using the non-linear estimation procedure. The computational formulae given by Equations 4.1 and 4.2 underestimated p(A) and bias compared with the nonlinear estimation (Equation 2.1) for both time ranges although the relative difference was maintained (p[A], 0.83 ± 0.01 for milliseconds compared with 0.92 ± 0.01 for seconds, $t[29] = 6.06$, $p < 0.01$). The PSE and difference limen were overestimated by the linear regression compared with the non-linear estimation, the PSE to a greater extent for milliseconds and the DL to a greater extent for seconds and as a consequence the Weber fractions obtained by linear regression were the same for each time range, 0.21 ± 0.01, $t(29) < 1$. Thus, the small but significant difference in Weber fractions between the time ranges was not maintained by the linear method with estimates midway between the values obtained by the non-linear estimation procedure (ie., slightly lower for milliseconds and slightly higher for seconds). The data points at the extremes of the psychophysical function are obviously important to accurate estimation of the parameters in Equation 2.1, and this is where important differences between the time ranges appear to occur (Figure 4.1C). However, although the linear method is only based on 3 data points and provides a less accurate method, the estimates seem adequate for comparisons within a time range when the non-linear method cannot be used.

Part 1: Cerebellar hemisphere and nucleus accumbens lesions

Training performance: Following surgery, overall performance decreased for all groups across both time ranges. For the millisecond range, mean performance was relatively poorer for both the HEM and NAC groups compared with the SHAM group, although this relative difference decreased with continued training (Figure 4.2A). These observations were confirmed by a Group (SHAM vs. NAC vs. HEM) x Block (Block 1, the last 6 training days preceding surgery, vs. Block 2, the first 6 days of post-surgery training, vs. Block 3, the last 6 days of post-surgery training) which showed a significant

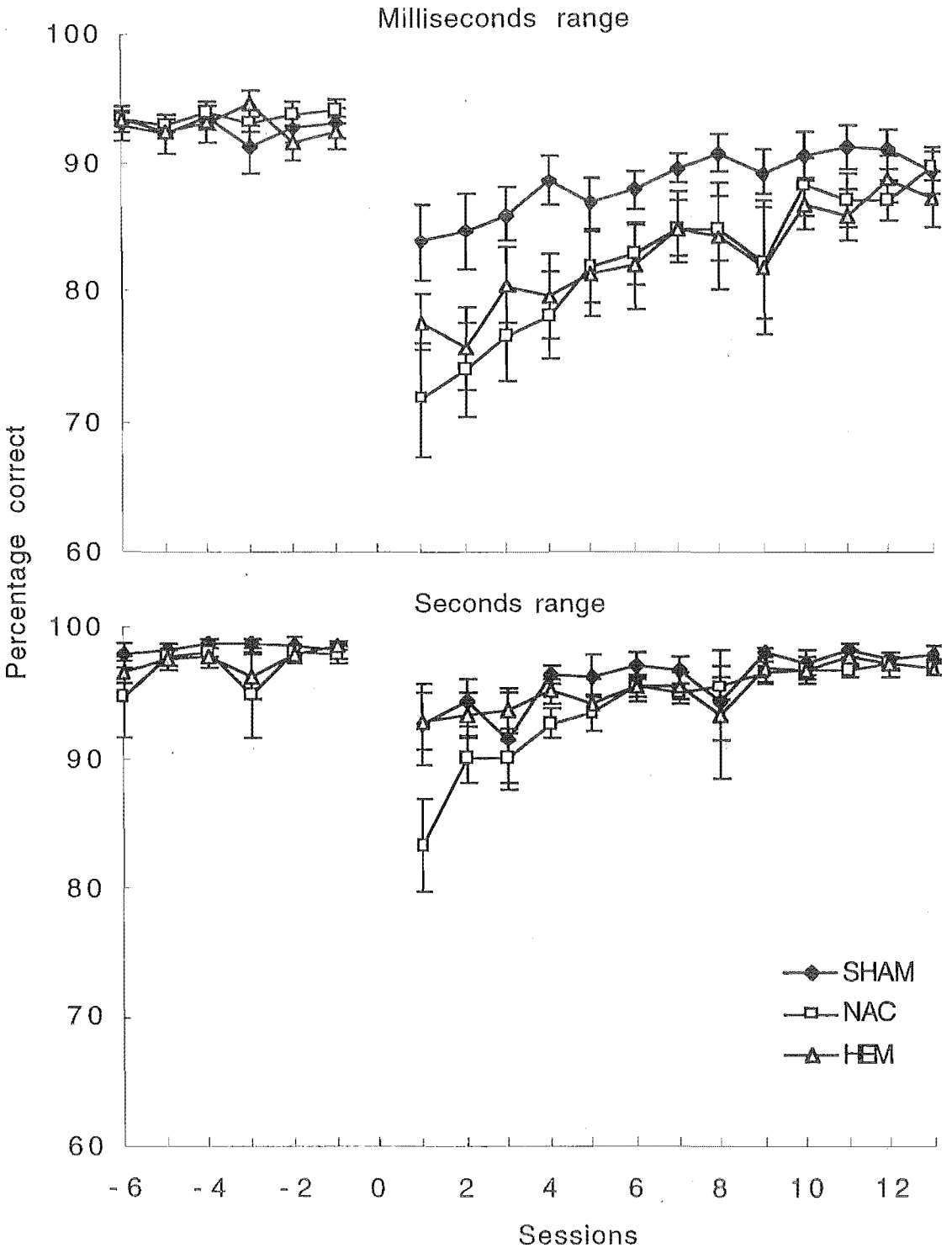

Figure 4.2. Percentage correct (±SE) as a function of preoperative (negative numbered sessions) and postoperative training sessions for the millisecond range (top panel) and seconds range (bottom panel) in Part 1. SHAM = sham lesioned group, NAC = nucleus accumbens lesioned group and HEM = cerebellar hemisphere lesioned group.

main effect for block, $F(2, 54) = 48.3$, $p < 0.01$, but not for group, $F(2, 27) = 1.9$ and a significant Group x Block interaction, $F(4, 54) = 2.9$, $p < 0.05$. A comparison of performance between each lesion group and the sham group revealed a significant difference between the NAC and SHAM group for Block 2, $F(1, 3) = 7.2$, $p < 0.02$, and a near significant difference in Block 3, $F(1, 3) = 3.3$, $p = 0.08$. The difference between the HEM and SHAM group approached significance in Block 2, $F(1, 3) = 3.7$, $p = 0.07$, and HEM group performance had also improved relative to the Sham group in Block 3, $F(1, 3) = 7.2$, $p = 0.09$.

In the seconds range, the drop in mean performance was similar for the HEM and SHAM groups but was lower initially for the NAC group (Figure 4.2B). However overall performance rapidly re-approached pre-surgery levels with further training. There was a significant main effect of block, $F(2, 54) = 26.2$, $p < 0.01$, reflecting poorer overall performance across groups after surgery but there was no main effect of group, $F(2, 27) = 1.7$, and no Group x Block interaction, $F(4, 54) = 1.7$.

The non-specific effect of surgery on overall performance was also reflected in an overall increase in the mean percentage of response latencies outside the 3 s criterion during training after surgery (less than 2.3% for Block 1 compared with less than 6% across Blocks 2 and 3).

First post-surgery bisection test (Post-surgery test 1): The main focus of Part 1 was the effects of cerebellar hemisphere and Nac lesions on timing performance during bisection testing, particularly changes in the Weber fraction after surgery. For post-surgery test 1, temporal discrimination was clearly disrupted in the NAC group compared with SHAM performance in both the millisecond and seconds range. HEM group performance was also clearly disrupted in the millisecond range but was similar to SHAM performance in the seconds range (Figure 4.3, middle panels). For the millisecond range, variance explained by Equation 2.1 was significantly lower for both lesion groups ($74 \pm 8\%$, $80 \pm 5\%$ for NAC and HEM groups, respectively) compared with the SHAM group in which variance explained remained at pre-surgery levels ($99 \pm 0\%$, $F(2,27) > 4.5$, $p < 0.03$). In the

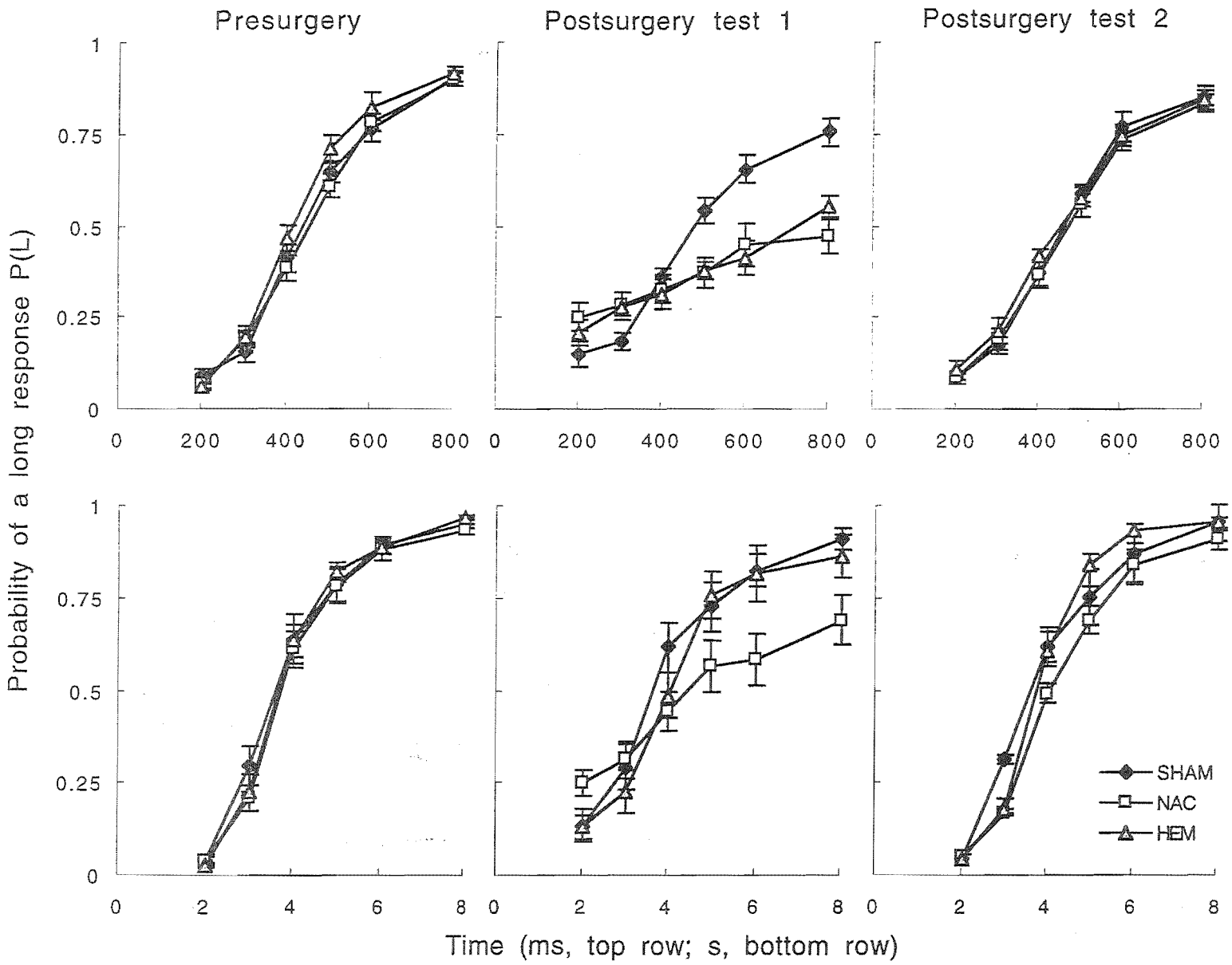

Figure 4.3. Mean probability of a long response (±SE) as a function of time (millisecond range top panels, seconds range bottom panels) for pre-surgery bisection tests (left panels), first post-surgery bisection test (middle panels) and second post-surgery bisection test. SHAM = sham lesioned group, NAC = nucleus accumbens lesioned group and HEM = cerebellar hemisphere lesioned group.

seconds range, variance explained by Equation 2.1 was also poorer for the NAC group (90 ± 3%) compared with the SHAM (97 ± 1%), and HEM groups (96 ± 2%) although this difference did not reach significance, $F(2, 27) = 2.26$. There was a significant increase in percentage of response latencies greater than 3 s postoperatively in the millisecond range for the HEM group from 4 ± 1% to 18 ± 5%, $F(1, 3) = 18$, $p < 0.01$ whereas there were no significant changes for the SHAM group from 3 ± 1% to 5 ± 2%, $F(1, 3) < 1$, and the NAC group from 3 ± 0% to 6 ± 1%, $F(1, 3) = 1.5$. Percentage of response latencies greater than 3 s did not increase significantly for the seconds range.

For the reasons explained in Data Analysis the subsequent comparisons of parameters obtained in post-surgery test 1 with parameters obtained in the pre-surgery test were based on estimates obtained by the computational formulae (Equations 4.1 and 4.2) and the linear regression method (Maricq & Church, 1983) using Group (SHAM vs. NAC vs. HEM) x Test (pre-surgery test vs post-surgery test 1) ANOVAs within each time range.

In the millisecond range, there were no differences between the groups in pre-surgery bisection testing for any of the parameters estimated, ($F[2, 27] < 1.74$, $p > 0.19$ (Figures 4.4 and 4.5, open bars, left panels). For the p(A) measure across pre-surgery and post-surgery tests, there were significant main effects for group, $F(2,27) = 7.23$, $p < 0.01$, test, $F(1, 27) > 220$, $p < 0.01$, and a significant Group x Test interaction, $F(2, 27)$ 15.9, $p < 0.01$. This interaction reflected the significantly poorer p(A) in post-surgery test 1 for both the HEM and NAC groups compared with the SHAM group, $F(1, 3) > 10.1$, $p < 0.01$, although p(A) for the SHAM group was also poorer compared to pre-surgery levels, $F(1, 3) = 14.7$, $p < 0.01$. The level of overall performance, post-surgery, was similar between the HEM and NAC groups, $F(1, 3) < 2.58$. There was a shift in bias towards the short lever across groups, $F(1, 3) = 12.5$, $p < 0.01$ but no significant effects of group, $F(1, 3) < 1$, and no significant Group x Test interaction, $F(1,27) < 1$ (Figure 4.4, bottom left panel).

There was also an overall increase in the PSE, $F(1, 27) = 14.4$, $p < 0.01$ across tests but no significant effect of group, $F(1, 27) = 2.24$, and no Group x Test interactions,

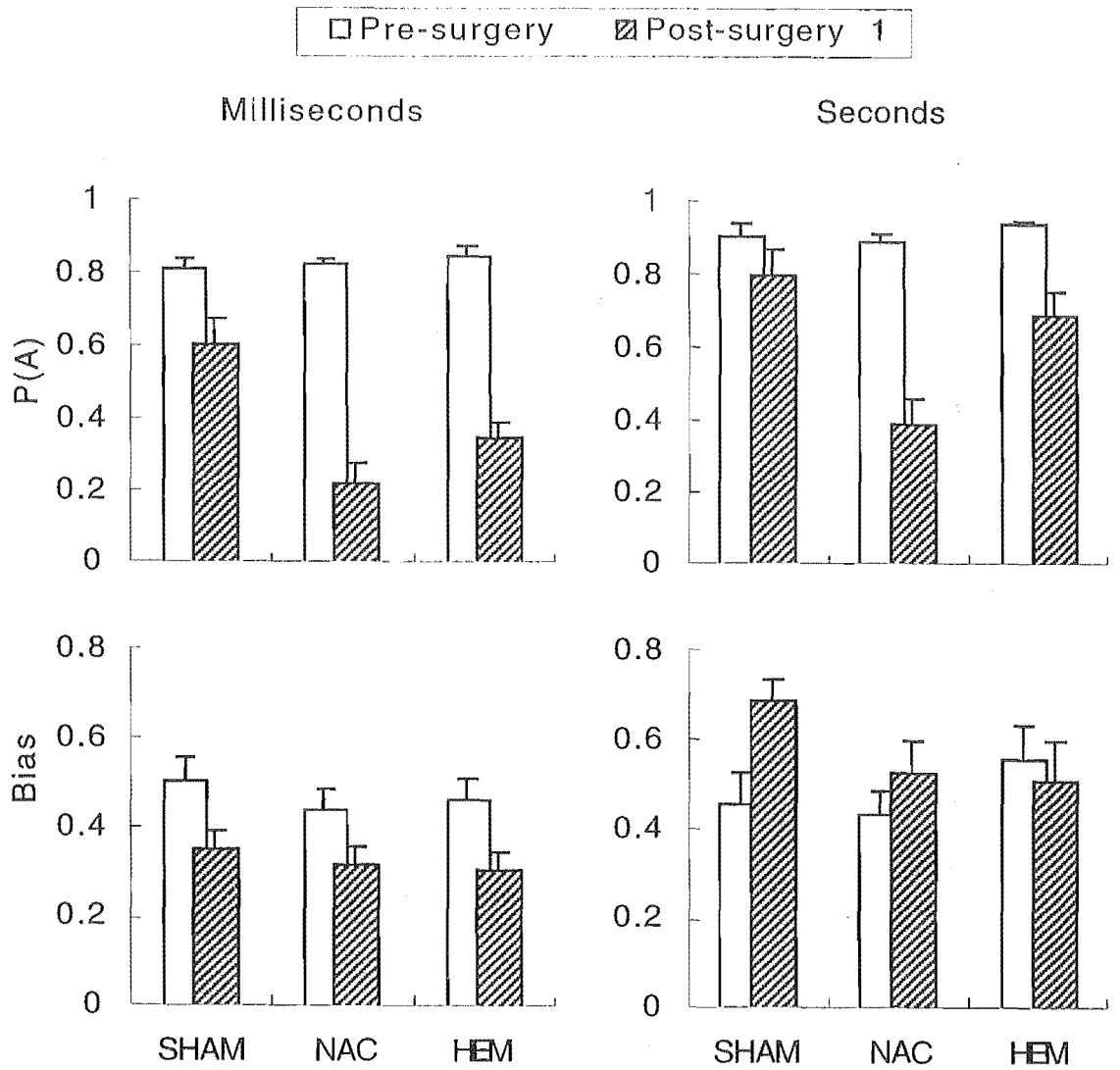

Figure 4.4. Mean (±SEM) p(A)s (top panels) and position bias (bottom panels) for millisecond (left) and seconds (right) range estimated by computational formulas for pre-surgery testing and the first post-surgery test in Part 1. SHAM = sham operated group; NAC = nucleus accumbens lesioned group; HEM = cerebellar hemisphere lesioned group.

$F(2, 27) = 1.97$, despite the increase in mean PSE being greatest in the NAC group and smallest in the SHAM group (Figure 4.5).

Although there appears to have been a substantial increase in the millisecond DL for both NAC and HEM groups relative to the SHAM group (Figure 4.5), the 2-way ANOVA revealed only a significant main effect of test, $F(1, 27)$ and no main effect of group, $F(2, 27) = 2.18$, $p = 0.13$ or Group x Test interaction, $F(2, 27) = 2.07$, $p = 0.15$, presumably because of the increased variability in DL for the NAC group especially.

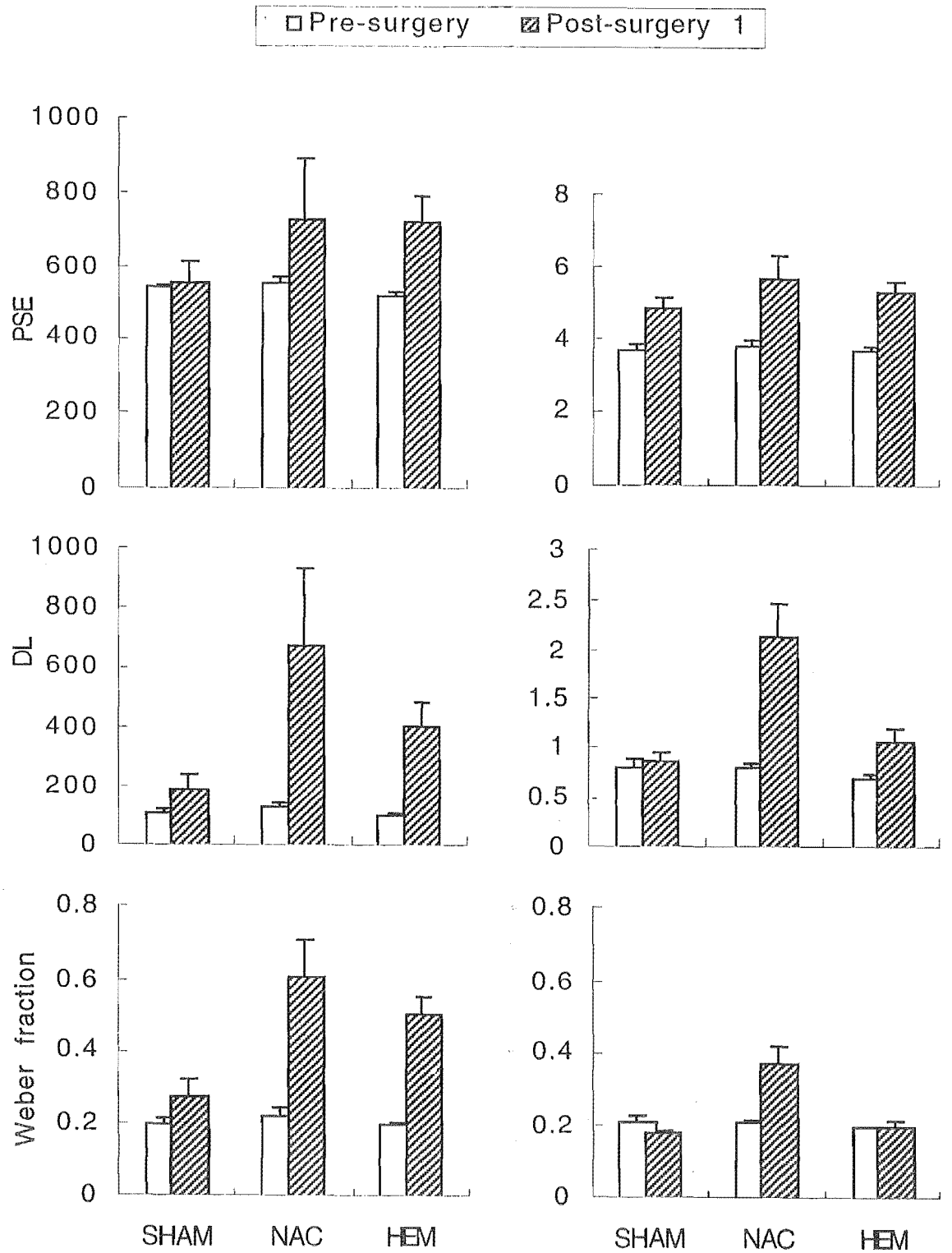

Figure 4.5. Mean (±SEM) PSE (top panels), DL (middle panels) and Weber fraction (bottom panels) for millisecond (left) and seconds (right) range estimated by linear regression for pre-surgery testing and the first post-surgery test in Part 1. PSE = point of subjective equality; DL = difference limen; SHAM = sham operated group; NAC = nucleus accumbens lesioned group; HEM = cerebellar hemisphere lesioned group.

For the millisecond Weber fraction, however, there was a significant main effect for group, $F(2, 27) = 4.64$, $p < 0.02$, and test, $F(1, 27) = 43.8$, $p < 0.01$ and a significant Group x Test interaction, $F(2, 27) = 5.43$, $p < 0.01$. The Weber fractions for NAC and HEM groups in the first post-surgery test were both significantly higher than the Weber fractions for the SHAM group, $F(1, 3) > 4.44$, $p < 0.04$, but did not differ significantly from each other, $F(1, 3) = 1.16$.

For the seconds range, there were no differences between the groups in pre-surgery bisection testing for any of the parameters estimated, ($F[2, 27] < 1.08$, $p > 0.35$ (Figure 4.4 and 4.5, right panels). Once more for p(A) across tests there was a significant main effect for group $F(2,27) = 4.54$, $p < 0.02$, test, $F(1, 27) > 48.6$, $p < 0.01$, and a significant Group x Test interaction, $F(2, 27)$ 6.04, $p < 0.01$. In contrast to the millisecond range, this interaction reflected a significantly poorer performance by the NAC group compared with both HEM and SHAM groups, $F(1, 3) > 4.6$, $p < 0.04$. The p(A) for the SHAM group did not differ significantly between pre-surgery and post-surgery tests and although overall performance by HEM group performance did drop postoperatively, HEM and SHAM group p(A)'s did not differ significantly in post-surgery test 1, $F(1, 3) = 1.22$ (Figure 4.4, top right panel). There was an overall increase in bias towards the long lever, most marked in the SHAM group although the 2-way ANOVA showed no significant main effect for group, $F(2, 27) < 1$, or test, $F(1, 27) = 3.9$, $p = 0.06$, and no significant Group x Test interaction, $F(2, 27) = 2.62$, $p > 0.09$. As in the millisecond range, there was an overall increase in PSE for post-surgery test 1, $F(1, 27) = 32.3$, $p < 0.01$, but no other significant effects (group, $F[1, 27] = 1$, Group x Test, $F[2, 27] < 1$, Figure 4.5).

The most striking result in the seconds range was the marked increase in variability of timing in the NAC group. For both DL and the Weber fraction there was a significant main effect for group, test and a significant Group x Test interaction (group, $F(2, 27) > 7.16$, $p < 0.01$, test, $F(1, 27) > 4.5$, $p < 0.05$, Group x Test, $F(2, 27) > 8.2$, $p < 0.01$. The Weber fraction and DL for the NAC group was significantly higher than the Weber fractions for either the HEM and SHAM groups, $F(1, 3) > 9.79$, $p < 0.01$ (Figure 4.5, middle and bottom, right panels).

Second post-surgery bisection test (Post-surgery test 2): The striking feature of the psychophysical functions generated for post-surgery test 2 is the apparent absence of any deficits in any group in either time range (Figure 4.3, right panels). Lesioned rats showed a substantial recovery in all aspects of performance and Equation 2.1 accounted for at least 98 ± 1% of the variance in all except the SHAM group for the seconds range (96 ± 2%). Variance explained did not differ from pre-surgery levels in both ranges (group, $F(2, 27) < 1$ for group, $F(1, 27) < 1$ for test). Overall percentage of response latencies greater than 3 s were still higher than preoperative levels in the millisecond range (test main

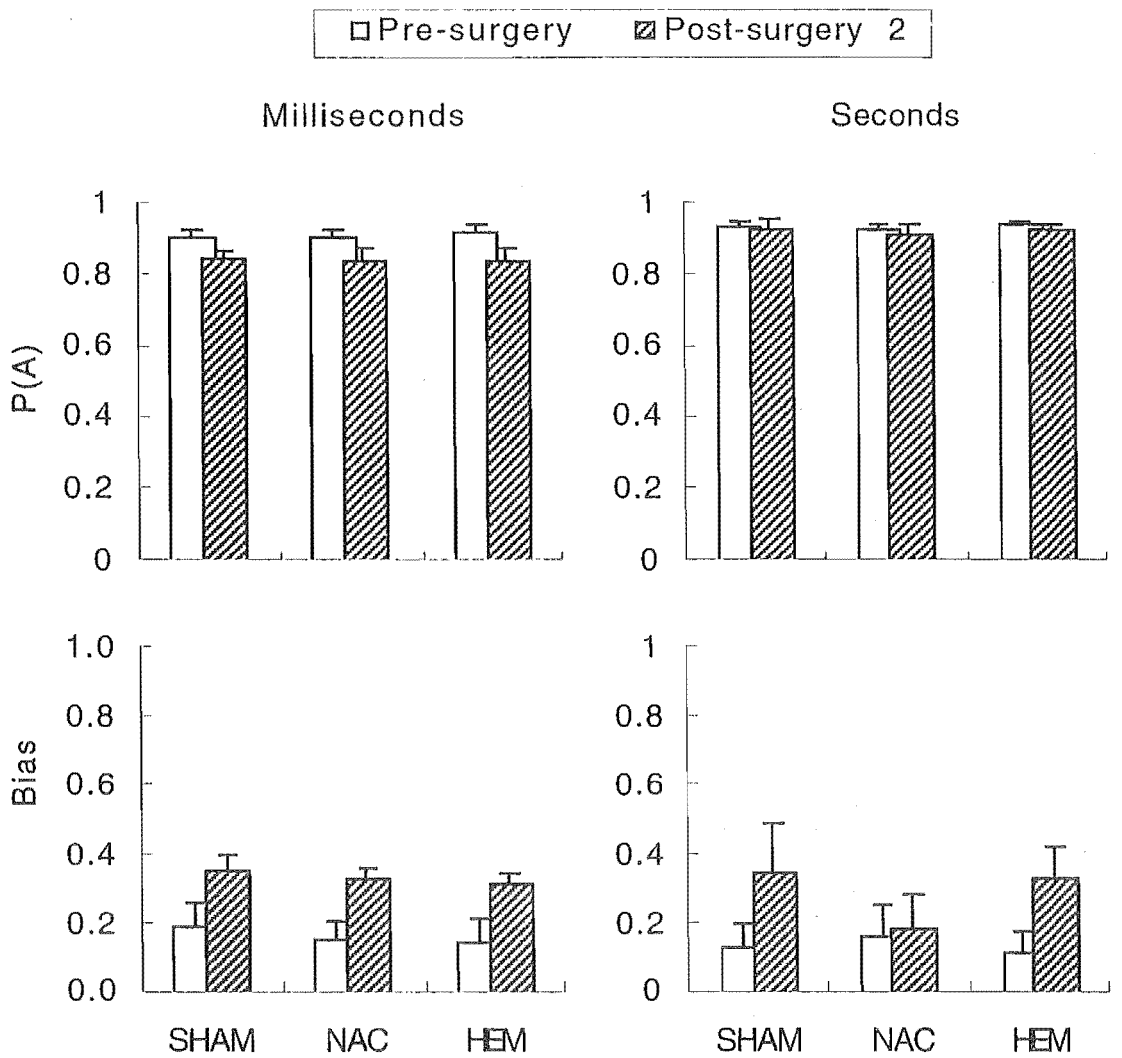

Figure 4.6. Mean (±SEM) p(A)s (top panels) and position bias (bottom panels) for millisecond (left) and seconds (right) range estimated by non-linear regression (Equation 2.1) for pre-surgery testing and the first post-surgery test in Part 1. SHAM = sham operated group; NAC = nucleus accumbens lesioned group; HEM = cerebellar hemisphere lesioned group.

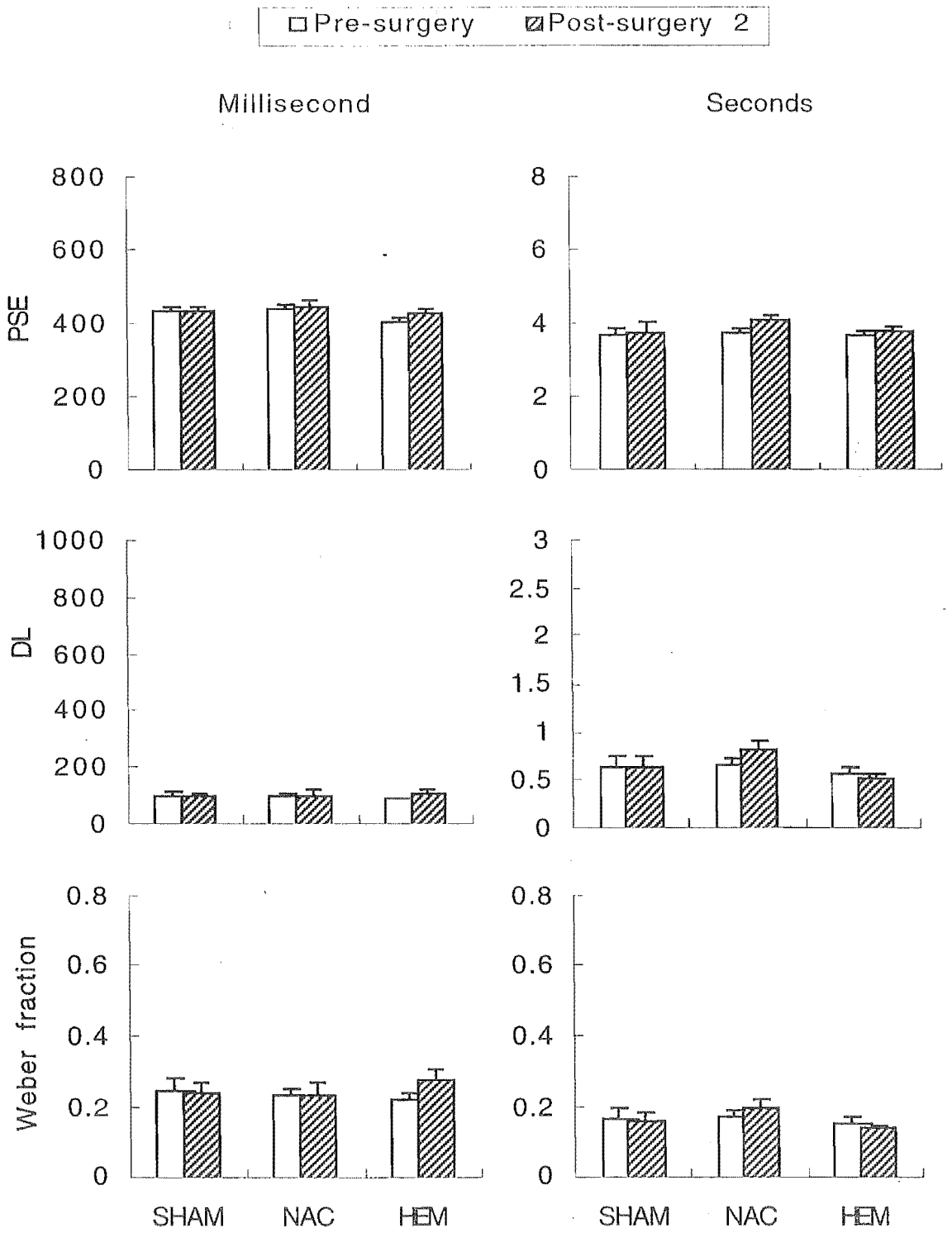

Figure 4.7. Mean (±SEM) PSE (top panels), DL (middle panels) and Weber fraction (bottom panels) for millisecond (left) and seconds (right) range estimated by non-linear regression (Equation 2.1) for pre-surgery testing and the first post-surgery test in Part 1. PSE = point of subjective equality; DL = difference limen; SHAM = sham operated group; NAC = nucleus accumbens lesioned group; HEM = cerebellar hemisphere lesioned group.

effect, $F[1, 26] = 5.4$, $p < 0.03$, main effect of group and Group x Test interaction, ns.) but did not differ from pre-surgery levels in the seconds range, $F(2, 26) < 1$, for group and Group x Test interaction, $F(1, 26) = 1.8$ for test.

For p(A) in the millisecond range there was a significant main effect of test $F(1, 27) = 11.1$, $p < 0.01$, reflecting slightly poorer overall performance across the groups (Figure 4.6). For all other parameters, there were no other significant main effects, $F(1, 27) < 2.49$, $p > 0.13$, and no significant interactions, $F(2, 27) < 1.54$, $p > 0.25$, in either time range (Figures 4.6 and 4.7).

Response latencies: The increase in percentage of responses excluded under the 3 s latency criterion for the HEM group in post-surgery test 1 prompted a closer examination of all response latencies in Part 1 (Figure 4.8). Across groups prior to surgery, the form of the mean response latency function across signal length for the seconds range was similar in form to those reported previously (e.g., Maricq & Church, 1983; Meck, 1983). The fastest response latencies occurred at the extremes (1.04 ± 0.04 s and 0.94 ± 0.05 s for 2 and 8 s signals, respectively) and the longest latency occurred at the geometric mean (1.40 ± 0.05 s at 4 s). The new finding in the current study was that response latency function for a millisecond range bisection was similar in form to the seconds range function. The shortest response latencies for the millisecond task were also at the extremes (1.14 ± 0.04 s and 1.04 ± 0.04 s for 200 and 800 ms signals, respectively) and the longest at the geometric mean (1.30 ± 0.05 s at 400 ms). A Range (millisecond vs seconds) x Length (2 to 8 s or 200 to 800 ms) ANOVA showed that mean latency across signal length did not differ between the two time ranges, $F(1, 26) < 1$. However, there was a main effect of length, $F(5, 130) = 29.9$, $p < 0.01$, and a significant Range x Length interaction, $F(5, 130) = 6.0$, $p < 0.01$. These effects occurred because the response latency function for the millisecond task was much flatter than the function for seconds. Millisecond range response latencies at the extremes were longer than seconds range response latencies at the extremes but the millisecond response latency was shorter than the seconds response latency at the geometric mean although the individual differences were not significant, $F(1, 3) < 3.0$.

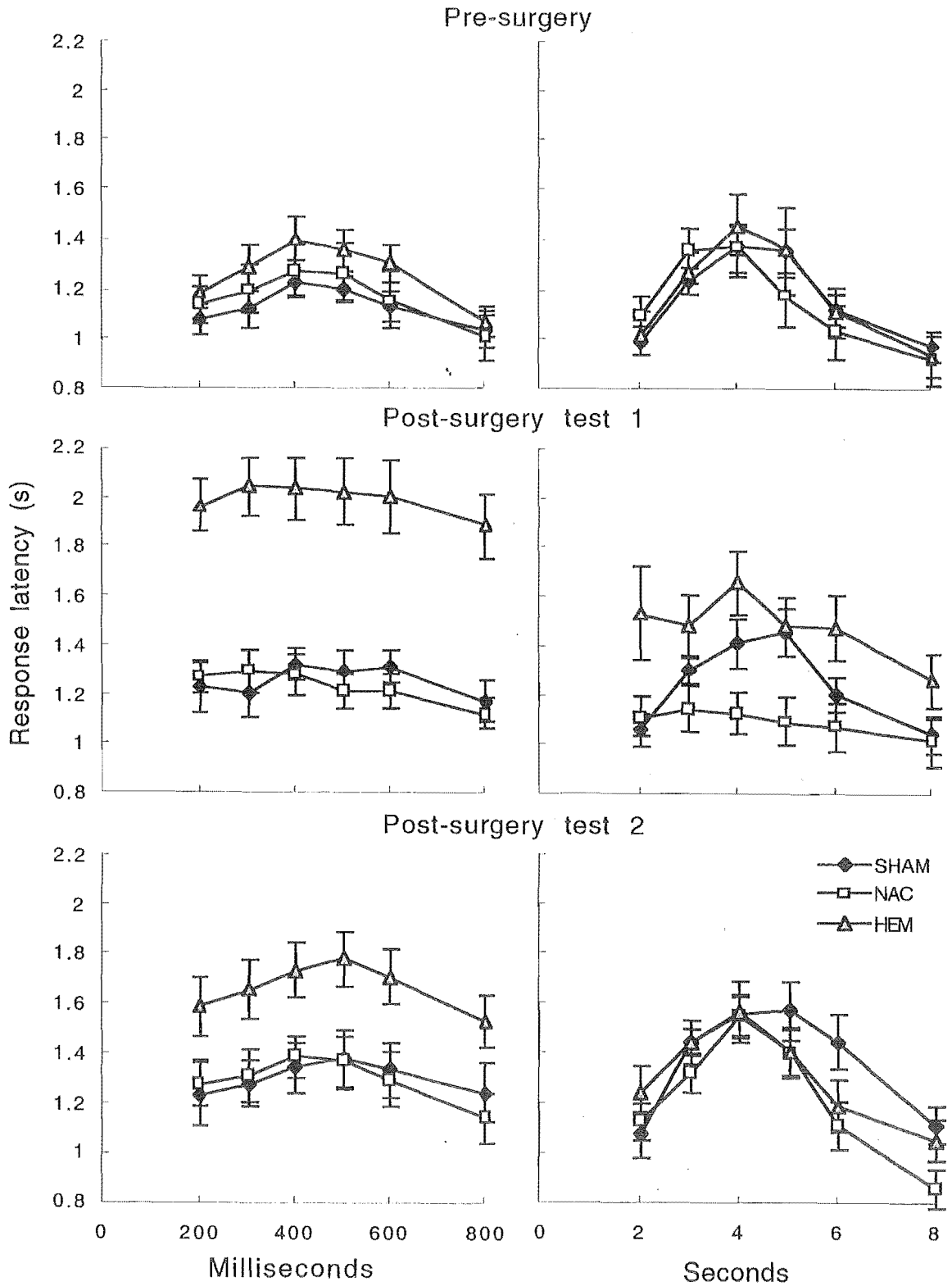

Figure 4.8. Mean response latency (±SE) as a function of signal duration (millisecond range left panels, seconds range right panels) for pre-surgery bisection tests (top panels), first post-surgery bisection tests (middle panels) and second post-surgery bisection tests (bottom panels). SHAM = sham lesioned group, NAC = nucleus accumbens lesioned group and HEM = cerebellar hemisphere lesioned group.

For the millisecond range, the most striking change in the response latency functions postoperatively was the increase in response latencies for the HEM group (Figure 4.8 middle and bottom left panels). A Group x Test (pre-surgery vs. post-surgery test 1 vs. post-surgery test 2) x Length ANOVA on these data revealed significant main effects for group, $F(2, 27) = 8.1$, $p < 0.01$, for test, $F(2, 54) = 31.5$, $p < 0.01$, and for length, $F(5, 135) = 28.5$, $p < 0.01$. There was also a significant Group x Test interaction, $F(4, 54) = 14.4$, $p < 0.01$. Response latencies for the HEM group were slower than those for the NAC and SHAM groups in both post-surgery tests (post-surgery test 1, $F[1, 3] > 36$, $p < 0.01$, post-surgery test 2, HEM vs NAC, $F[1, 3] = 5.9$,$p < 0.02$, and HEM vs SHAM, $F[1, 3] = 3.7$, $p = 0.06$). Response latencies increased significantly within the HEM group for post-surgery test 1 compared to preoperative levels, $F(1, 3) = 110.8$, $p < 0.01$ and although there was a significant improvement by post-surgery test 2 compared with post-surgery test 1, response latencies for the HEM group were still significantly slower than in the pre-surgery test, $F(1, 3) > 23.9$, $p < 0.01$. The response latencies also appeared to increase for the NAC and SHAM groups postoperatively but these increases were non- significant, $F(1, 3) < 2.9$, $p > 0.1$, except for the increase in response latencies that the SHAM group in post-surgery test 2 approached significance compared to preoperative response latencies, $F(1, 3) = 3.9$, $p = 0.06$. There was also flattening of response latencies functions in post-surgery test 1 as reflected in a significant Test x Length interaction, $F(10, 270) = 2.9$, $p < 0.01$.

For the seconds range, the most striking feature of the response latency functions is the flattening of these functions in post-surgery test 1 for both the NAC and HEM groups. In post-surgery test 1, the response latencies for the NAC group were faster whereas the response latencies for the HEM group were slower than those for the SHAM group. However, the 3-way ANOVA showed only the significant main effect of length, $F(5, 120) = 36.9$, $p < 0.01$, as expected and a significant Test x Length interaction, $F(10, 240) = 3.9$, $p < 0.01$. The main effect of test approached significance, $F(2, 48) = 2.4$, $p = 0.10$ because response latencies tended to be slower overall in both post-surgery tests but there was no main effect of group, $F(2, 24) = 2.2$, no Group x Test, $F(4, 48) < 1$, or Group x

Length interaction, $F(10, 120) < 1$, and no significant 3-way interaction, $F(20, 240) = 1.27$.

Response latencies during millisecond bisection testing in Part 2 of Experiment 3.1 were also examined (these data were not available for Part 1 of Experiment 3.1) but unlike the effects found in Experiment 4 there were no significant differences between the groups. In Experiment 3.1 overall mean response latency was 1.4 ± 0.1 s for the SHAM group, 1.6 ± 0.1 for the VERM group, and 1.6 ± 0.1 for the HEM group.

Part 2: 100 - 400 and 300 - 1200 ms timing and 1- 4 s and 3 to 12 s timing.

In Part 2 the rats all learned the new temporal discriminations extremely quickly. Rate of acquisition and asymptotic performance could not be estimated because too few data points were available but visual inspection of the data suggested no obvious differences between the groups.

Bisection testing: For the bisection data in Part 2 all parameters were estimated using Equation 2.1. Performance in the 100 to 400 ms time range was analysed first with 1-way ANOVA's to determine if any deficits in timing performance were evident at these very short durations before examining performance across time ranges. This analysis revealed that there were no significant differences between groups for any of the parameters estimated, $F(2, 26) < 2.14$, although the DL and Weber fractions appeared higher for the NAC and HEM groups (74 ± 10 and 71 ± 10 ms, respectively, for DL; 0.31 ± 0.04 and 0.28 ± 0.03, respectively, for Weber fraction) compared with the SHAM group (DL = 47 ± 8 ms and Weber fraction = 0.21 ± 0.04). The mean variance accounted for by Equation 2.1 was greater than $96 \pm 1\%$.

The parameters estimated from individual psychophysical functions across the time ranges were analyzed by Group x Range (100 to 400 ms vs. 300 to 1200 ms vs. 1 to 4 s vs. 3 to 12 s) ANOVA's. For P(A), there was a significant main effect of range, $F(3, 78) = 21.0$, $p < 0.01$, reflecting the relatively poorer performance in the shortest time

range but there was no main effect for Group, $F(2, 26) < 1$, and no Group x Range interaction, $F(6, 78) < 1$ (Figure 4.9, top panel). For PSE, there was also a significant main effect of range, $F(3, 78) = 1130$, $p < 0.01$, as expected, and a significant Group x Range interaction, $F(6, 78) = 2.522$, $p < 0.03$, but no main effect for group, $F(2, 26) = 1.29$ (Figure 4.9, middle panel). The PSE was significantly higher for the NAC group in the 300 to 1200 ms range compared with both HEM and SHAM groups, $F(1, 3) = 5.1$, $p < 0.03$. For the HEM group, the PSE in the 100 ms to 300 ms range was also higher compared to the SHAM group, although this difference only approached significance, $F(1, 3) = 3.0$, $p = 0.10$. In contrast, the HEM group PSE was significantly lower compared with the SHAM group in the 3 to 12 s range, $F(1, 3) = 4.42$, $p < 0.05$. Otherwise, there were no significant or near significant differences in PSE.

The DL for both the NAC and HEM groups appears higher in the millisecond range (100 to 400 ms and 300 to 1200 ms) but similar or lower in the seconds range (1 to 4 s and 3 to 12 s) compared with the SHAM group (Figure 4.9, bottom panels). For DL the main effect for group approached significance, $F(2, 26) = 2.63$, $p = 0.09$, but there was no significant Group x Range interaction, $F(6, 28) = 1.65$, $p = 0.15$.

The Weber fraction was highest for the shortest time range (100 to 400 ms) and decreased as the time range increased (Figure 4.10), as predicted by the generalised Weber function, although for the SHAM group the function was almost flat. For Weber fraction, there was a significant main effect of range, $F(3, 78) = 10.56$, $p < 0.01$, but there was no significant main effect for group, $F(2, 26) = 1.35$. The Group x Range interaction approached significance, $F(6, 78) = 1.97$, $p = 0.08$ because although the Weber fraction tended to be higher for NAC and HEM groups for the shorter time ranges compared to the SHAM group, they were similar or lower than the SHAM group at the longer time ranges. Simple main effects for group across the time ranges confirmed this impression. For the SHAM group, the Weber fractions were similar across times ranges, $F(3, 78) < 1$. In contrast, there was a significant increase in Weber fraction as the time range became shorter for the NAC and HEM groups $F(3, 78) > 6.8$, $p < 0.01$. To explore the effects of sample size and the power of detecting a significant Group x Range interaction, the data from each

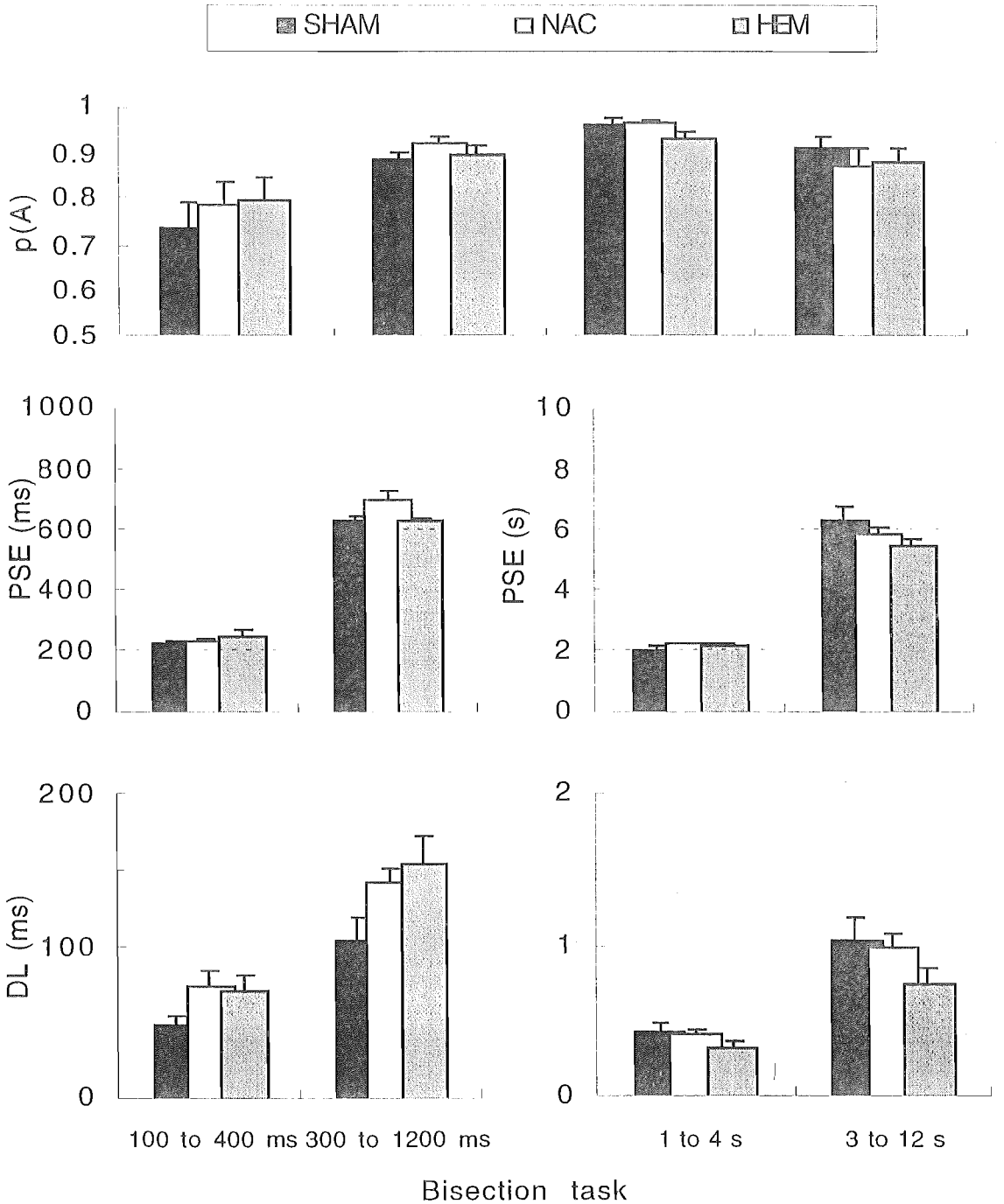

Figure 4.9. Mean (±SEM) P(A) (top panels), PSE (middle panels, the dashed line is the geometric mean of each time range) and DL (bottom panels) in Part 2. SHAM = sham operated group; NAC = nucleus accumbens lesioned group; HEM = cerebellar hemisphere lesioned group.

rat was duplicated so that there were now double the number of rats in each group and these data were re-analysed. As a consequence of the increased sample size the Group x Range interactions for DL and Weber fraction were both significant, $F(6, 165) > 4$, $p < 0.01$.

The relationship between estimated parameters and time range was of particular interest in the HEM and SHAM groups because of the specific predictions made with regard to hemisphere lesion's influence on performance. For this reason performance between these 2 groups was compared using Group (HEM vs SHAM) x Range ANOVAs. Once more, the only significant effect for p(A) was the main effect of range, $F(3, 48) = 15.0$, $p < 0.01$. For PSE there was no main effect of group but there was a main effect of range, $F(3, 48) = 616$, $p < 0.01$, and, more importantly, a Group x Range interaction, $F(3, 48) = 4.26$, $p < 0.01$ because the PSE for HEM was relatively longer at the shortest range (100 to 400 ms) and relatively shorter at the longest range (3 to 12 s) compared with SHAM group PSE. There was a similar relationship for DL, with the HEM group showing relatively more variability in the millisecond range (100 to 400 ms and 300 to 1200 ms) and relatively less in the seconds range (1 to 4 s and 3 to 12 s). The main effect of group approached significance, $F(1, 16) = 3.5$, $p = 0.08$ and there was a main effect of range, $F(2, 48) = 61.8$, $p < 0.01$ and a near significant Group x Range interaction, $F(6, 78) = 1.97$, $p = 0.08$. This pattern of change in variability across time ranges was also reflected in the Weber fraction. There was no main effect of group, $F(1, 16) < 1.0$ but there was a significant main effect of range, $F(3, 48) = 4.5$, $p < 0.01$, and a significant Group x Range interaction, $F(3, 48) = 2.0$, $p < 0.05$.

Although it was intended to estimate the level of constant variance using the generalised Weber function (Equation 1.2), the rats' sensitivity to time was far greater than that indicated by the earlier work of Church et al (1976). In fact, there was no significant difference in Weber fraction across time ranges from 100 ms to 12 s for the SHAM group in Part 2. As a consequence, the estimates of constant variance were very unreliable with the standard errors that were larger than the estimate in nearly every case. The mean asymptotic Weber fraction (or Weber constant) obtained in this way was lowest for the HEM group, 0.13 ± 0.02, compared with 0.16 ± 0.02 and 0.17 ± 0.02 for the NAC and SHAM rats but there were no significant differences, $F(2.26) < 1.8$. The asymptotic estimates are consistent, however, with the significant trends in DL and Weber fraction revealed by the ANOVAs, above, and reflect the shape of the curves in Figure 4.10.

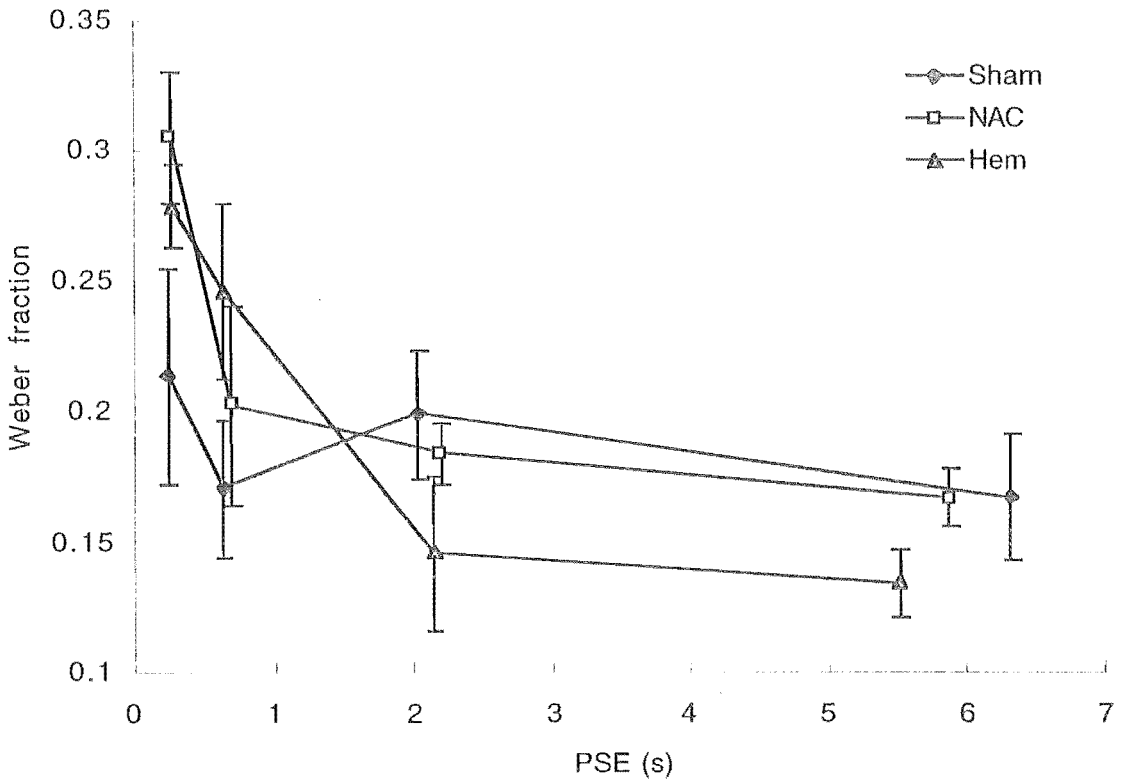

Figure 4.10. Mean (±SEM) Weber fraction as a function of the PSE for each time range in Part 2. PSE = point of subjective equality; DL = difference limen; SHAM = sham operated group; NAC = nucleus accumbens lesioned group; HEM = cerebellar hemisphere lesioned group.

Response latencies: Figure 4.11 shows the changes in response latency functions across the bisection conditions in Part 2. The curves appear flattest in the shortest time range and become progressively more peaked as the time range becomes longer, replicating the preoperative finding. Once again the most striking feature is the longer response latencies for the HEM group in the millisecond time ranges compared to both NAC and SHAM groups. A Group x Range (100 to 400 ms vs. 300 to 1200 ms vs. 1 to 4 s vs. 3 to 12 s) ANOVA revealed a significant main effects of group, $F(2, 26) = 4.3$, $p < 0.03$, and range, $F(3, 78) = 26.4$, $p < 0.01$, and a significant Group x Range interaction, $F(3, 78) = 5.5$, $p < 0.01$. Simple main effects across range for the SHAM group confirmed that mean response latencies did not change across time range, $F(3, 78) < 1$. However, there were significant, but quite different changes in mean response latency across range for both the NAC and HEM groups, $F(3, 78) > 12.1$, $p < 0.01$. For the NAC group, mean response latencies were faster than SHAM group latencies in both seconds

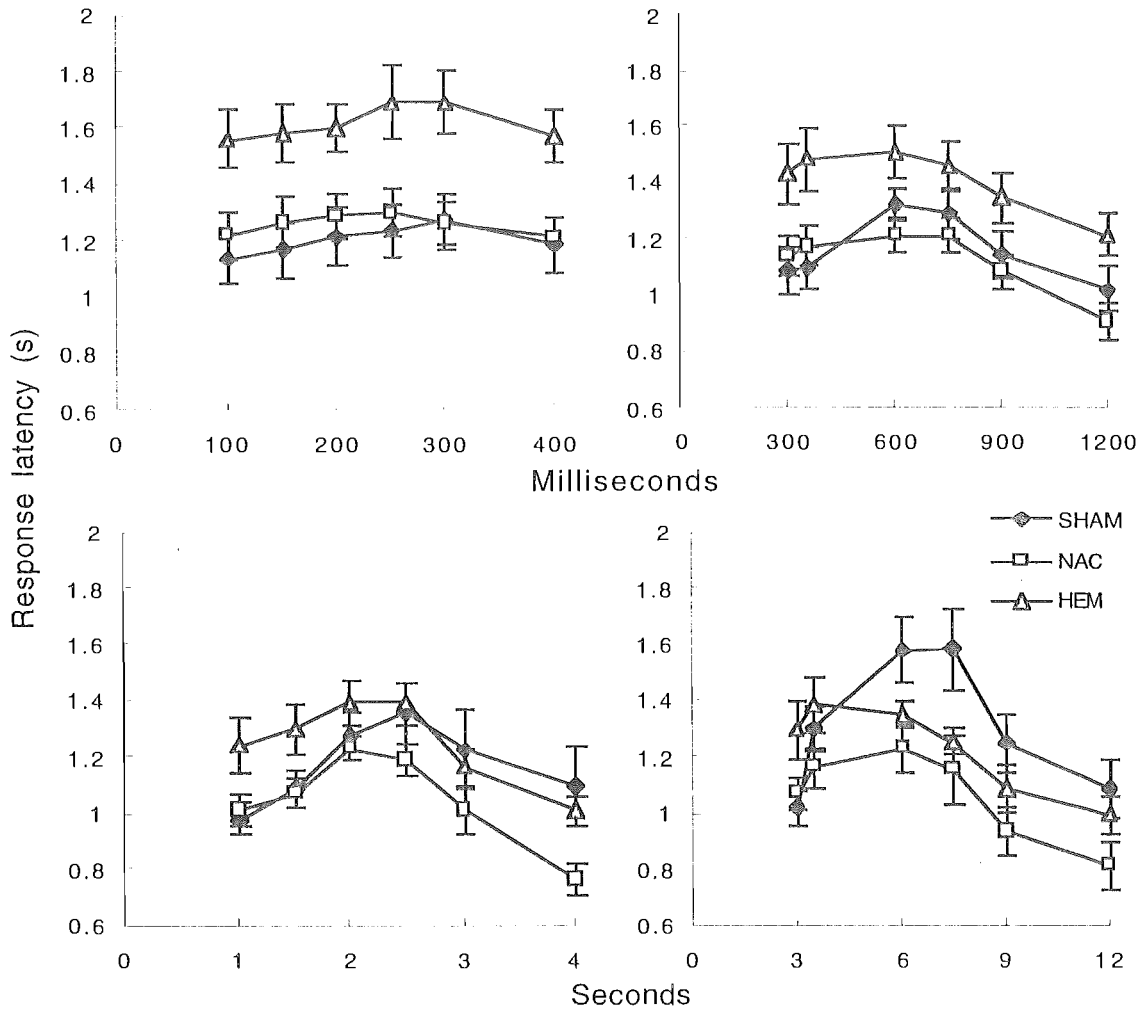

Figure 4.11. Mean response latency (±SE) as a function of signal duration for millisecond range bisection tasks (top panels) and seconds range bisection tasks (bottom panels). SHAM = sham lesioned group, NAC = nucleus accumbens lesioned group and HEM = cerebellar hemisphere lesioned group.

range conditions (1 to 2 s, $F(1, 3) > 2.9$, $p = 0.10$; 3 to 12 s, $F(1, 3) > 3.8$, $p = 0.06$) but similar to SHAM group latencies in both millisecond range conditions (100 to 400 and 300 to 1200 ms, $F(1, 3) < 1$). In contrast, for the HEM group, mean response latencies were significantly slower than SHAM group latencies in both millisecond range conditions (100 to 400 and 300 to 1200 ms, $F(1, 3) > 5.0$, $p < 0.04$) but the same as SHAM group latencies in both seconds range conditions (1 to 2 s and 3 to 12 s, $F(1, 3) < 1$).

Histology.

Figure 4.12 shows reconstructions of the smallest and largest cerebellar and NAC lesions. In the cerebellar hemisphere lesions, Crus 1, Crus 2 and the simplex lobules were

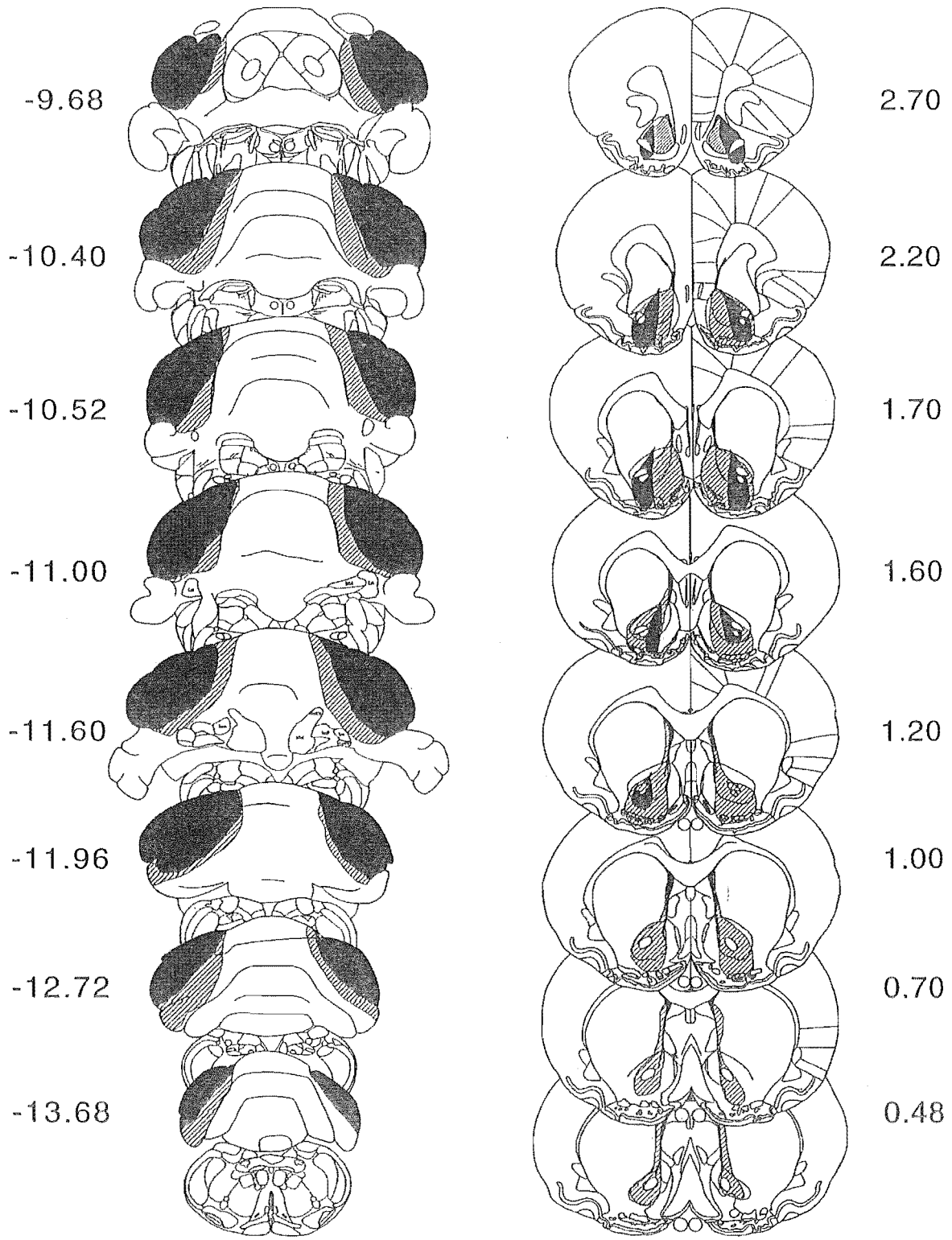

Figure 4.12. Reconstructions of the smallest (solid) and largest (hatched) cerebellar hemisphere (left) and nucleus accumbens (right) lesions. Coronal sections are adapted from Paxinos and Watson (1986) and coordinates are mm from bregma.

almost completely destroyed (mean 99%, 93%, and 94%, respectively) and there was substantial damage to the paramedian lobules (mean 56%). There was also some damage to the lateral portions of lobules 4 and 5 (mean 22%). There was very little damage to other regions of the cortex (mean < 6%) or to cells in the dorsal dentate-interpositus nuclei complex (mean 6%). Overall, the hemisphere lesions in Experiment 4.1 tended to be more anterior, with slightly more damage to the simplex lobules and the lateral regions of lobules 4 and 5 and slightly less damage to the paramedian lobules, than the hemisphere lesions in Experiment 3.1. However, the lesions were very similar otherwise, ablating most of the cerebellar hemispheres except for the most anterior and posterior regions (i.e., lateral portions of lobules 2 and 3 and the copula pyramis, respectively).

Lesion boundaries in the NAC group were identified on the basis of cell loss and gliosis as assessed by comparison with the brains of sham rats under light microscopy. All NAC rats sustained damage to the ventral striatum (NAC, olfactory tubercle, and ventral pallidum). There was considerable loss of tissue from the accumbens core (23% to 76%) and the shell region (11% to 56%). In the rats with the largest lesions, the ventricles were noticeably enlarged (7 rats) and there was some encroachment into adjacent areas such as the ventral pallidum and olfactory tubercle. In both the NAC and HEM groups no relationship between the behavioural measures and lesion extent or damage to particular structures was observed.

Discussion

The most striking finding of the current experiment was the dissociation between the effects of cerebellar hemisphere and NAC lesions on timing performance across the millisecond and seconds range conditions in the initial post-surgery bisection test in Part 1. The cerebellar hemisphere lesions produced a marked disruption for millisecond range timing in overall performance, as measured by p(A), and in terms of variability, as measured by the DL and Weber fraction, whereas seconds range timing was unimpaired.

Nucleus accumbens lesions also produced a marked disruption in temporal discrimination, but these rats showed similar deficits in both millisecond and seconds range timing. For the seconds range, p(A) was significantly lower and DL and Weber fractions significantly higher than in both hemisphere and sham lesioned rats. Equally impressive was the recovery in performance by both lesion groups by the second post-surgery test, when all aspects of temporal discrimination performance were the same between groups and no different to pre-surgery performance with the exception of overall performance in the millisecond range which was lower to an equal extent for all groups compared to pre-surgery levels.

The dissociation between NAC and hemisphere rats across time ranges during postoperative training was similar to that in the postoperative bisection tests. For postoperative millisecond range training, both cerebellar hemisphere and NAC lesioned rats showed a much lower percentage correct than sham rats, initially, and a gradual improvement with subsequent training. For the seconds range, percentage correct was similar for hemisphere and sham rats but was lower at the start of training and showed rapid recovery for the NAC rats. Performance during postoperative training also highlights a small non-specific surgery effect on p(A) across groups and time ranges in the first post-surgery bisection test. However, it is important to note that for sham rats there were no differences between pre-surgery and initial post-surgery bisection test levels of DL and the Weber fractions. Also, p(A) is a measure of overall performance that is independent of measures such as DL and Weber fraction which reflect variability in timing (Blough, 1996). The dissociation between millisecond and seconds range timing in hemisphere and NAC lesioned rats also suggest that these results were not due to a differential impact of any non-specific effects in lesioned rats.

Preoperative behaviour in the current study showed that rats acquired a seconds range discrimination more rapidly than a millisecond range discrimination and that asymptotic performance was higher for seconds range timing compared with millisecond range timing. There were also other differences between millisecond and seconds range performance during psychophysical testing. In Part 1, the Weber fraction (or coefficient of variation)

was higher for the millisecond range compared to the seconds range and the PSE was above the geometric mean for the millisecond range bisection but below the geometric mean for seconds range timing. However, it should also be noted, as mentioned earlier, that although there was a difference between the Weber fractions for the millisecond range and seconds range during early performance in the bisection task, the Weber fractions in the millisecond range became more similar to the Weber fractions in the seconds range with continued training. In Part 2 the Weber fraction did not differ significantly for sham operated rats between 100 ms to 12 s, a finding that is consistent with the millisecond timing performance of pigeons (see Section 1.1.3). The preoperative response latency functions also suggest that similar processes underlie millisecond and seconds range timing. The millisecond range response latency function was flatter than the seconds range response latency function, but in both time ranges response latencies were shortest at the extremes and longest at the subjective middle. The nature of these curves is discussed further in Chapter 5.

An unexpected finding in Part 1 of the current experiment was the impact of cerebellar and NAC lesions on response latency functions. In the first post-surgery bisection test hemisphere rats were much slower to respond than either NAC or sham rats in the millisecond range. The hemisphere rats' response latencies also tended to be longer than NAC rats' latencies in the seconds range.

There also appeared to have been a flattening of response latency curves for both lesion groups in both time ranges. Both slower response latencies and flatter curves have been reported previously with dopaminergic drugs (Maricq & Church, 1983) but never for rats with cerebellar lesions. The flattening effect of both hemisphere and NAC lesions was particularly noticeable in the seconds range where the sham rats' response latency function has a clear characteristic shape.

Despite the substantial recovery in temporal discrimination performance in the second post surgery bisection test, response latencies during millisecond range testing for the hemisphere rats remained significantly longer than NAC and sham rats. However, there were no overall differences in response latency functions for the seconds range, and for

both time ranges the characteristic shape of the functions was now clearly evident across groups.

The relationship between longer latencies and temporal discrimination performance may be difficult to interpret. Given the well known cerebellar involvement in the motor domain and the fact that response latencies are significantly longer for hemisphere rats even after recovery of millisecond timing performance, it is most likely that response latencies primarily reflect motor deficits rather than any underlying cognitive deficits and are not directly related to the impaired temporal discrimination performance in the first post-surgery bisection test.

In Part 2 overall performance as measured by p(A) decreased significantly across rats as the time range became shorter but there were no group differences. There was, however, evidence for lasting, but subtle, lesion effects on interval timing across the millisecond and seconds domain and these are summarised in Table 4.1. For the hemisphere group, PSE, DL, Weber fraction and response latency were all higher than sham group levels in the millisecond range whereas PSE, DL and Weber fraction were all lower than for sham rats in the seconds range, but overall response latencies were the same. This pattern of change for DL and Weber fraction across time range for hemisphere rats was in contrast to the pattern of Weber fractions found in sham rats across the 4 bisection tests.

Statistical tests within the shortest duration bisection condition revealed no significant differences in sensitivity although the mean Weber fraction for the hemisphere group was

Table 4.1
Relative change in parameters estimated and mean response latencies in Part 2 of Experiment 4.1 for the NAC and HEM groups compared to the SHAM group.

Bisection task	PSE		DL		Weber fraction		Mean response latency	
	HEM	NAC	HEM	NAC	HEM	NAC	HEM	NAC
100 to 400 ms	↑	-	↑	-	↑	-	↑	-
300 to 1200 ms	-	-	↑	-	↑	-	↑	-
1 to 4 s	-	-	↓	-	↓	-	-	-
3 to 12 s	↓	-	↓	-	↓	-	-	-

Note. Light/dark arrows indicate parameter values relative to the appropriate SHAM group value. PSE = point of subjective equality; DL = difference limen.

higher than that for the sham group. This finding may be related to sample size and suggests that larger groups than those traditionally used in lesion work may be needed in future studies. It may also be useful to test rats with cerebellar lesions at even shorter durations than those used in the current study.

The trend in Weber fraction across time range for the hemisphere lesioned rats in Part 2 is consistent with the idea that a reduction in scalar variance may have been compensating for an increase in constant variance. A higher DL and Weber fraction in conjunction with a longer PSE in the millisecond range and a lower DL and Weber fraction in the seconds range is entirely consistent with higher constant variance in conjunction with lower scalar (memory/comparator) variance, although it is not clear why the PSE should be lower than the sham group PSE in the seconds range. Killeen, Fetterman & Bizo (1997) have analyzed the predicted location of the PSE on the basis of signal detection theory and the generalised Weber function. For short durations where constant variance dominates, the PSE approaches the arithmetic mean whereas for longer durations the PSE should be greater than the harmonic mean (twice the reciprocal of the sum of the reciprocals of the extremes) by some proportion that depends on the Weber constant and the ratio of the extremes. This means that for longer durations the PSE lies between the harmonic mean and the geometric mean (square root of the product of the extremes; harmonic mean < geometric mean < arithmetic mean). Experimental manipulations that add constant noise or increase the Weber fraction will move the PSE towards the arithmetic mean whereas decreases in Weber fraction or a reduction in the ratio of the extremes (i.e., with standards that are closer together) will move the PSE towards the harmonic mean (Killeen et al, 1997).

For a reduction in scalar variance to compensate for increased constant variance the relative contribution of constant variance would have to be similar or less than scalar variance in the millisecond time ranges tested in the current study. For example, the levels of constant variance in well trained rats may be closer to the levels estimated for pigeons (17 ms, see Killeen et al, 1997). There was some support for this suggestion in the current finding that with sufficient training rats' timing performance in the millisecond range

approached the level shown by pigeons (i.e., a constant Weber fraction down to approximately 100 ms, see Section 1.1.3).

For Part 2, the NAC group also showed changes in performance across time range. The PSE, DL and Weber fraction for the NAC group tended to be higher than sham group levels at the shortest durations but, in contrast to the hemisphere group, performance did not differ from sham group performance in the seconds range conditions. This pattern of results suggests that the NAC lesioned rats were unable to improve their timing performance for very short durations, unlike the sham group. Interestingly, response latencies for the seconds range bisection tasks were significantly faster for the NAC lesioned rats.

In conclusion, the current results replicate Clarke et al's (1996) findings that timing performance in the millisecond range but not the seconds range is disrupted by damage to the lateral cerebellum and that these deficits are relatively transient. The current findings also suggest that cerebellar damage adds constant noise to interval timing which results in a compensatory reduction in scalar variance. This interpretation favours the constant variability hypothesis because there is no reason to expect any change in seconds range timing performance with the millisecond timer hypothesis. The absence of any cerebellar effects on variability in seconds range timing provides no support for the scalar variability hypothesis. The initial impact of NAC lesions on both millisecond and seconds range timing is tentative support for a single timing system responsible for millisecond and seconds range timing. However, it does not appear that the NAC is directly involved in interval timing processes and there was no support for Rammsayer's (1997) hypothesis that the mesolimbic system is preferentially involved in seconds range timing compared to millisecond range timing.

Chapter 5

General Discussion

5.1 The Main Issues

The focus of the current thesis was the psychological and neurobiological processes responsible for interval timing. The central question was whether an independent timing mechanism based in the cerebellum is responsible for both motor and interval timing in the millisecond range, or whether a distributed timing system described by the mode-control model provides a basis for both millisecond and seconds range timing. The proposed cerebellar involvement in interval timing provided the neurobiological basis of the thesis. The mode-control model of timing provided the main theoretical context for the thesis because it provides an excellent account of interval timing over a wide variety of timing procedures. A quantitative description of this model (Gibbon, 1991) also converges on the generalised Weber function which provides a parsimonious account of timing across both millisecond and seconds ranges. Furthermore, Section 1.4 provided an extension to counting of Gibbon's (1991) quantitative analysis of timing and suggested a unique approach to the study of cerebellar involvement in timing processes.

Recent reports of temporal processing deficits in humans and animals with cerebellar damage, in addition to evidence from imaging studies of cerebellar activation during interval and motor timing, suggest that the cerebellum is involved in timing. Three possibilities concerning the role of the cerebellum in the processing of temporal information have been considered in this thesis. The first was Ivry and colleagues' original contention that the cerebellum provides an independent millisecond timing system for both motor and perceptual domains. I have referred to this as the millisecond timer hypothesis. A more recent suggestion by Gibbon et al (1997),

which I have referred to as the scalar variability hypothesis, suggests that the cerebellum is part of an extended neural system, including DA and ACh pathways, which is described by the mode-control model. In this view, damage to the cerebellum contributes scalar variance to the timing process irrespective of time range. The third proposal, developed in this thesis, is similar to Gibbon et al's (1997) view that the cerebellum is part of a distributed system that provides the neural basis for the mode-control model. However, this third view of cerebellar involvement in timing, the constant variability hypothesis, proposes that the cerebellum is associated with a source of constant variance in timing. In a more specific form, the constant variability hypothesis elaborates the suggestion made by Nichelli (1993) that cerebellar damage adds noise to switch processes during interval timing. It was this last suggestion that led to the novel prediction that cerebellar damage should disrupt counting in animals.

The potential involvement of the cerebellum in counting processes prompted the examination of numerical discrimination in Chapter 2. This chapter addressed several important behavioural and theoretical issues regarding the relationship between counting and timing in rats. The main concern was that non-numerical cues associated with the periodic signals routinely used in previous psychophysical studies of counting by animals may have been confounded with number. This issue was important in the current context for two main reasons. First, these previous studies provide important empirical support for the event mode of the mode-control model of timing and counting upon which the specific form of the constant variability hypothesis is based. Second, the non-numerical cues that are associated with periodic signals may have fallen within the domain of cerebellar function, making any disruption of numerical discrimination by cerebellar lesions difficult to interpret. Not directly related to the lesion work in this thesis, but with important theoretical implications for animal counting, was the relative salience of time and number for rats.

5.2 Empirical Contributions of the Current Research

The contributions of the current research are two-fold. There were several new behavioural findings regarding the relationship between timing and counting in Chapter 2; and Chapter 4 extended our knowledge of temporal discrimination in rats for durations less than 1 s. The neurobiological findings in Chapters 3 and 4 favoured the constant variability hypothesis over the millisecond timer hypothesis, and provided no support for the scalar variability hypothesis.

5.2.1 Behavioural findings

The main contribution of Chapter 2 was to show that rats can count events that occur at irregular intervals even when the stimulus pattern is unique at every presentation. There was no decline in asymptotic performance for numerical discrimination when the periodic event sequences were abruptly changed to unique sequences. The Weber fraction for number obtained during bisection testing with unique signals was also similar to that obtained during bisection testing with periodic signals. Furthermore, there was little systematic relationship between performance of the numerical discrimination of unique sequences and the deviation of either temporal ratios and sequence patterns from the corresponding periodic signal. Experiment 2.3 showed that naive rats trained with unique signals could attain a level of performance similar to rats trained with periodic sequences. The unique signals provide numerical cues that minimise unwanted confounds with number. Thus Chapter Two's findings showed that numerical discrimination is not based on temporal ratio or stimulus pattern and provided a clear demonstration that rats can count sequential events.

An unexpected result was the failure to replicate Meck and Church's (1983) finding that both time and number gained control of choice behaviour following training with compound

standards. However, a closer examination of the data from the only study claiming to have replicated Meck and Church's (1983) Experiment 1 suggests that for these pigeons (Roberts & Mitchell, 1994), as for the rats in Experiment 2.1, time rather than number gained control of choice behaviour during training with compound standards.

Experiment 2.4 provided further evidence that time has a relatively greater influence on choice behaviour than number. Despite extensive training with separate signals for both time and number, rats responded exclusively on the basis of time when presented with conflicting temporal and numerical cues and inaccurate temporal cues continued to influence choice behaviour even in the presence of accurate numerical cues. In contrast, temporal ratio and stimulus pattern did not appear to gain control of choice behaviour even though these cues were also accurate predictors of the reinforced choice. The more rapid acquisition of the temporal discrimination compared with the numerical discrimination in Experiment 2.3 also suggests the total sequence duration is a more salient cue than number of events. Overall, these results suggested that rats will only use numerical cues in the absence of more salient temporal cues and supported Davis and Memmott's (1983) last resort hypothesis.

The preoperative behaviour reported in Chapter 4 and the performance by the sham rats postoperatively provided an opportunity to compare millisecond range timing with seconds range timing. The rats clearly acquired the seconds range bisection task more rapidly and asymptotic performance was better than for the millisecond range. The psychophysical functions failed to superpose in real time or subjective time, although the latter transformation approached superposition, and the Weber fraction was significantly higher for the millisecond range than for the seconds range.

The similarity in Weber fractions across the range from 100 ms to 12 s for sham rats in Part 2 of Experiment 4.1 suggests that with sufficient training rats' sensitivity to time improves for shorter durations. This improvement in variability for the millisecond range, in the absence of reductions in variability in the seconds range, implies a reduction in constant noise. In addition, the relative differences in PSE between the millisecond range and the seconds range in Chapter 4 replicated sham performance in Chapter 3. The PSE for the 200 to 800 ms bisection was higher than the geometric mean (400 ms), as it was in Part 2 of Chapter 3, whereas the PSE

for seconds range timing throughout this thesis has tended to fall at or below the geometric mean (4 s). The relative position of the PSE for the 100 to 400 ms bisection in Part 2 of Chapter 4 was similar to that found for the 200 to 800 ms bisection in Part 1, whereas for the remaining bisection tasks in Part 2 (300 to 1200 ms, 1 to 4 s and 3 to 12 s) the PSE moved progressively closer to the geometric mean. These relative differences in PSE are consistent with Killeen et al's (1997) analysis of the location of the PSE within the context of the generalised Weber function. According to the generalised Weber function, and on the basis of Killeen et al's analysis of the location of the PSE, both the higher PSE and Weber fraction in the millisecond range are indicative of the relatively greater influence of constant variance on overall variability in millisecond range timing.

Another novel finding in the current work was the similarity in the response latency functions across signal length in both the millisecond and seconds time ranges (Chapter 4). This result provides further evidence of a similarity in the processes underlying millisecond and seconds range timing. Latencies were shortest at the reinforced extremes and longest at the subjective middle (i.e., geometric mean). The form of the response latency function has not been explained (Maricq & Church, 1983; Meck, 1983), although it may reflect either the physical demands of the task, some underlying cognitive process or a combination of both. Meck (1983) has suggested that latency may be inversely related to the animals' expectation of reinforcement. However, the physical demands of the bisection task have an obvious impact on responding in the seconds range. At the onset of a signal, rats start pawing at the short lever slot and a response is invariably made if the signal stops and the lever extends. If the signal continues, the rat moves across the operant box to start pawing at the long lever slot. In the seconds range, the rat may be between levers with intermediate durations but is usually poised to respond following one of the extreme signals. Thus, the peaked form of the response latency function may reflect underlying decision processes or expectation of reinforcement that is accentuated by the physical demands of the task. In the millisecond range, the longest standard (800 ms) was similar in duration to the fastest response latency, greatly increasing the possibility that the levers are extended before the rat has prepared itself to respond. Thus, the latency at each point on the millisecond range response latency curve should reflect a similar amount of locomotor activity

whereas response latencies for seconds range timing reflect a relatively small motor component at the extremes compared to intermediate durations. This could explain the flatter response latency functions for the millisecond range where the overall shape may more accurately reflect any underlying cognitive processes and the overall mean response latency may more accurately reflect locomotor contributions.

The rats' preoperative behaviour in Chapter 4 was of interest because very little behavioural evidence from animals supports the notion of separate interval timers for the millisecond and seconds range. Previous psychophysical studies with animals (e.g., Church et al, 1978; Fetterman & Killeen, 1992) suggest that differences between millisecond range and seconds range timing performance are consistent with the increased influence of constant variance at millisecond range durations in a timing mechanism that spans both millisecond and seconds ranges. The higher Weber fraction and PSE for the millisecond range in Experiment 4.1 supports this proposal and the form of the response latency functions also suggests that a similar set of processes underlie temporal information processing in both time ranges. These behavioural findings provide only weak evidence, at best, for separate millisecond and seconds range timing mechanisms. Instead, the generalised Weber function appears to be a more parsimonious description of interval timing across milliseconds and seconds.

5.2.2 Neurobiological findings

Before discussing the neurobiological findings of the current thesis, it may be helpful to review the predictions made by each of the three hypotheses that were considered in this thesis. These predictions were: for the millisecond timer hypothesis, that millisecond timing but not seconds range timing or counting should be disrupted; for the scalar variability hypothesis, that numerical discrimination and temporal discrimination in both time ranges should be disrupted; and for the constant variability hypothesis, that numerical discrimination should be disrupted and that millisecond range timing should be impaired whereas seconds range timing should be spared. The counting prediction of the constant variability hypothesis follows from a specific

form which posits central switch processes as the source of constant variance increased by cerebellar damage. The constant variability hypothesis also entertains the notion that compensatory changes within the mode-control model may be evident in seconds range timing. For example, increased efficiency in a part of the timing system contributing to scalar variance might be able to compensate for an increase in constant variance. If this was the case, deficits in millisecond timing might be difficult to detect but a relative decrease in scalar variance should be evident in the seconds range.

For rats with lesions to the cerebellar hemispheres, there was no evidence of any postoperative increase in the variability for seconds range timing. In both Experiments 3.1 and 4.1, overall performance by hemisphere rats was similar to sham performance. In Experiment 3.1, there appeared to be a marked drop in p(A) for the first post-surgery test although this was not replicated in Experiment 4.1 and in neither experiment were the differences significant. There was no other evidence of disruption to any other aspect of temporal discrimination in the seconds range by rats with cerebellar hemisphere lesions in either experiment.

In the millisecond range, however, performance by hemisphere lesioned rats did show some disruption. For a millisecond discrimination task acquired preoperatively, there was initial impairment in overall performance and an increased variability in timing, followed by relatively rapid recovery in both these aspects of temporal discrimination (Chapter 4). However, further testing over four additional bisection tasks in a range from 100 ms to 12 s revealed some longer lasting effects of cerebellar hemisphere lesions. There was no evidence that overall performance (i.e., p[A]) was impaired but the Weber fraction and PSE tended to be higher for the hemisphere rats at the shortest durations and lower at the longest durations compared with performance in the sham group. A similar result for their consistency score was reported by Clarke et al (1996) across the millisecond and seconds bisection tasks in their first experiment. Those results and the current findings are consistent with the suggestion that cerebellar hemisphere lesions add constant variance to interval timing and that this induces a compensatory increase in efficiency for other parts of the timing system.

In contrast to the preoperatively acquired millisecond range discrimination, overall performance but not rate of acquisition was impaired during training for a millisecond

discrimination task acquired postoperatively but the only significant difference in performance during bisection testing was a lower PSE compared to vermis and sham lesioned rats (Chapter 3). It is possible that the impaired overall performance was related to the postoperative acquisition of the task but the lower PSE in Part 2 of Experiment 3.1 is more difficult to explain because PSE tended to be higher in the millisecond range for hemisphere rats in Part 2 of Experiment 4. A lower PSE (relative to control subjects) was also found in an analogous 100 to 900 ms bisection task with cerebellar patients (Nichelli et al, 1996) but that study also found no differences in two other millisecond range bisection tasks. Like the rats in Part 2 of Chapter 3, these cerebellar patients acquired the task with existing and presumably long-standing cerebellar damage. However, Clarke et al (1996) also found that their bias score, which confounds PSE and position bias, was lower for hemisphere rats in the millisecond range immediately after surgery in their first experiment but failed to replicate this finding in the second experiment. Overall, these results suggest that the PSE does not provide a particularly consistent evidence for cerebellar deficits in millisecond range timing. Changes in PSE associated with cerebellar damage need to be treated cautiously in the absence of any other deficits. It is important to note that the PSE does not provide a direct measure of variability, although it may reflect underlying changes in variability (see Discussion, Chapter 4).

Cerebellar hemisphere rats also showed some impairment in a numerical discrimination task (Chapter 3). Immediately following surgery there was an increase in the Weber fraction and an indication that p(A) decreased; overall performance and the Weber fraction returned to presurgery levels with additional training. Unlike the cerebellar hemisphere rats, the vermis and sham lesioned rats showed a reduced Weber fraction for number at the completion of postoperative training, to the same level as that for time. Within the context of the mode-control model, the improvement shown by vermis and sham lesioned rats must have been due to a decrease in a non-scalar source of variance because the Weber fraction for the concurrent temporal discrimination was unchanged. This finding suggests that with sufficient training rats are able to reduce constant variance associated with numerical discrimination of unique event sequences but cerebellar hemisphere lesions impede these improvements in sensitivity to

number. There was no evidence that hemisphere rats' performance was related to the brevity of events that comprised the signals.

One striking aspect of cerebellar hemisphere lesions was the recovery shown after the initial marked impairment in numerical discrimination (Experiment 3.1) and in the preoperatively acquired millisecond discrimination (Experiment 4.1). These results replicate those reported in the only other study to have examined the effects of cerebellar hemisphere lesions on millisecond timing (Clarke et al, 1996). Clarke et al (1996) also found recovery in performance with lesions to the lateral cerebellar nuclei which they ascribed to functional reorganization within the intact cerebellum after "extensive training". However, although the training rats receive may seem extensive for humans this is not necessarily so for the rats. For example, the amount of postoperative training received by the rats in the preoperatively acquired millisecond discrimination in Part 1 of Experiment 4.1 (7 sessions with approximately 220 reinforced trials per session, total = 1540) was almost identical to Clarke et al's (1996) rats (7 sessions with approximately 225 reinforced trials in each session, total = 1575). For the numerical discrimination in Part 1 of Experiment 3.1 the amount of training was much less (6 sessions with approximately 110 reinforced trials per session, total = 660). By comparison, the hemisphere rats in Part 2 of Experiment 3.1 required over twice as many trials before performing accurately in the postoperatively acquired millisecond range task (35 sessions with approximately 220 trials per session, total = 7700, with mean percentage correct at over 80% for over half these trials). Thus, hemisphere lesioned rats in the preoperatively acquired tasks in the current thesis (number, Experiment 3.1; millisecond time, Experiment 4.1) hardly received extensive training. Taking the amount of training into account along with the relatively short amount of time that had passed since surgery and the large size of the aspiration lesions (90% of the lateral cerebellar cortex was destroyed) it is unlikely that recovery in performance was due to a functional reorganization of the cerebellar cortex. However, compensatory mechanisms or some form of functional reorganization, or a combination of both, within an extended timing system may account for the recovery of performance shown by cerebellar hemisphere lesioned rats. For the postoperatively acquired millisecond discrimination, some form of functional reorganization was more likely because training began sometime after the rats had received their lesions and postoperative

training was necessarily more extensive than for the preoperatively acquired millisecond discrimination. The amount of training and the extended recovery period for these hemisphere lesioned rats may account for the different results in millisecond range timing performance in Part 2 of Experiment 3.1 and Experiment 4.1.

Response latencies were significantly longer in hemisphere rats than in sham rats for millisecond discriminations (100 to 400 ms, 200 to 800 ms, and 300 to 1200 ms) throughout Experiment 4.1, although the hemisphere rats showed no overt signs of motor impairment. It is most likely that these latencies are related to the physical demands of the bisection task rather than cognitive impairments because the shape of the response latency function was similar to that for sham rats. Also, in a recent study of appetitive signalled barpressing (SBP), rats with lesions to the dentate-interpositus complex showed normal bar-pressing 300 to 600 ms after the onset of a tone (Steinmetz, Logue, & Miller, 1993). This result suggests that there was no impairment in processing the auditory signal or in lever pressing behaviour and, further, Steinmetz et al's fast response latencies indicate that cerebellar lesioned rats do not have attentional difficulties. The main difference between the SBP task and the millisecond bisection task is that rats do not have to choose between two levers and can position themselves near the manipulanda in the SBP task. The increased response latencies shown by cerebellar rats in Experiment 4.1 may be due to a locomotor impairment or a cognitive impairment related to choice behaviour. However, as there was no other evidence of impaired choice behaviour (i.e., increased scalar variance that could arise from deficits in a comparator mechanism), the former interpretation is preferred. Response latencies were not recorded in Part 1 of Experiment 3.1 and response latencies were similar for all rats during millisecond range testing in Part 2 of Experiment 3.1.

Lesions to the cerebellar vermis, unlike hemisphere lesions, produced overt signs of motor impairment and, like hemisphere lesions, reduced the level of photocell cage activity following surgery. However, vermis lesions did not disrupt numerical discrimination or temporal discrimination in the seconds range, except for an initial drop in p(A), and produced no impairment for a millisecond range discrimination acquired postoperatively. This was an important result because it was possible that any type of brain damage might add constant

variability to millisecond timing, at least initially. It is still possible that the drop in p(A) represents the impact of lesions in general because there was some indication of lower p(A) immediately after surgery for all lesions in the current thesis. However, DL and Weber fraction were unimpaired by cerebellar vermis lesions which suggests that the deficits found with cerebellar hemisphere lesioned rats were related to the locus of the lesion and not to cerebellar (or other brain damage) in general.

Rats with NMDA lesions to the NAC showed an initial disruption to temporal discrimination. The pattern of marked deficits, followed by relatively rapid recovery, was similar to that shown by the hemisphere lesioned rats except that for the NAC rats both millisecond range and seconds range timing were disrupted. There was no suggestion of dissociation across time range between any aspect of temporal discrimination within the NAC group; overall performance dropped in both the millisecond and second ranges and variability increased in both the millisecond and seconds ranges. In addition, although NAC rats appeared to show complete recovery in temporal discrimination, some subtle residual effects were apparent across the 4 bisection tasks in the 100 ms to 12 s range. The NAC rats had a higher Weber fraction at shorter durations but similar Weber fractions at the longer durations compared with sham rats. This finding reflected an improved sensitivity for sham rats in the millisecond range, and suggested that the NAC rats were unable to make similar improvements in the acuity of their timing. Also in contrast to hemisphere rats, changes in response latencies for the NAC rats were shorter than controls across millisecond and seconds ranges in the first post-surgery test session in Part 1 of Experiment 4.1 and in the seconds range bisection tasks in Part 2.

5.2.3 Theoretical Implications of the Current Research

The findings in Chapter 2 had important implications for the event-mode as the means of enumeration. Broadbent et al (1993) have proposed a connectionist model of timing and counting, with two possible methods of accommodating numerical discrimination. One possibility was a mechanism similar to the event-mode in the mode-control model of timing and

counting whereas the other was based on a temporal ratio. It was suggested that if a temporal ratio provided the basis for numerical discrimination then periodic events should be counted with greater accuracy than events that occur at irregular intervals (Broadbent et al, 1993). The data in Experiments 2.2 do not support this prediction, and suggest that a process similar to the event mode provides the basis for numerical discrimination.

Overall, the results in Chapter 2 suggested a modification to the mode-control model of timing and counting. In the original form, temporal and numerical information are processed in parallel from the clock stage to the decision stage. Roberts and Mitchell (1994) suggested that temporal and numerical information could have separate representations in working memory although in their proposal comparisons with values stored in reference memory continue to be made in parallel at the decision stage. The modification proposed in Chapter 2 retains the concept of parallel processing of temporal and numerical information up to and including the accumulator/working memory stage. It was suggested, however, that at the decision stage, this information is processed sequentially with comparisons between accumulator values and cue information in reference memory made in descending order of salience. This modification can account for the overshadowing effect in Experiment 2.1 and the stronger control of behaviour by time found throughout Chapters 2 and 3.

There was little evidence in the current thesis to support the millisecond timer hypothesis. Although there was marked initial disruption following cerebellar hemisphere lesions there was also relatively rapid recovery and any lasting effects were quite subtle. It would seem reasonable to expect marked and lasting deficits in interval timing in the millisecond range following bilateral lesions to the lateral cerebellar cortex if this were the primary site for millisecond timing (Keele & Ivry, 1987; Ivry et al, 1988; Ivry & Keele, 1989; Keele and Ivry, 1990). A recent elaboration of the proposed functional organisation for a cerebellar based millisecond timer provides the basis for a useful analogy between lesions to the cerebellar cortex and lesions to the primary visual cortex. Ivry (1996) proposed that the cerebellar based timer is quite different from clock based models such as the mode-control model. In this highly speculative account he suggests that cortical columns aligned along one axis in the cerebellar cortex are tuned to different millisecond intervals whereas cortical columns along the orthogonal axis are tuned to domain

specific targets in the same way that orientation and ocular dominance are represented in the primary visual cortex (Ivry, 1996, see figure 2, p. 854). However, although bilateral destruction of 90% of the primary visual cortex results in a complete and permanent loss of vision (Kandel, Schwartz, & Jessel, 1991) perhaps with some residual capabilities, for example blindsight, analogous lesions to lateral cerebellar cortex in the current study produced only temporary deficits (not total loss) in millisecond timing followed by near complete recovery. Furthermore, the current findings are quite unlike those found following other brain lesions that show a marked degree of localisation of function. For example, aspiration lesions of the lateral cerebellar cortex completely and permanently abolish the ipsilateral conditioned eyeblink response (see Thompson, 1991). Lesions to the CPu and SN appear to result in the complete and permanent loss of seconds range interval timing (Meck, 1996). Therefore, given the current results it is unlikely that an independent millisecond timer is localised in the lateral cerebellum and other evidence that has been advanced to support the notion of a independent millisecond timer should treated somewhat sceptically.

Evidence of correlations across motor and interval timing tasks in the millisecond range merely indicate a common source of noise and do not offer any strong support for an independent millisecond timer. Studies of interval timing in humans with cerebellar damage are also inconclusive. Ivry and Keele (1989) reported disrupted millisecond range timing but did not test interval timing in the seconds range. Nichelli et al (1996) found increased variability in a seconds range bisection task and a millisecond range task but failed to find any evidence of increased variability in two other millisecond range tasks. Although, temporal aspects of conditioned responding are disrupted by cerebellar damage, this is not surprising considering the extensive evidence which suggests that the CR memory trace is localised in the cerebellum (Thompson, 1991). Imaging studies do not provide unequivocal support for an independent millisecond timer because they show activation of both the cerebellum and basal ganglia during temporal processing tasks.

The deficits in interval timing following NAC lesions are consistent with limbic involvement in memory/comparator processes within the mode-control model because both millisecond and seconds range timing were effected (Part 1, Experiment 4.1), although it is

possible that these deficits mask any increase in constant variance. However, the NAC does not appear to play a critical role in interval timing because the only lasting deficit was an inability to improve the Weber fraction in the millisecond range with additional training (Part 2, Experiment 4.1). These deficits may have been related to disruption of NAC efferents to frontal regions that are known to be involved in interval timing. There was no evidence in the current study that any of the timing deficits found following the NAC lesions were associated with motivational factors, although the traditional view is that the NAC is involved in motivational processes. A more recent interpretation of the non-temporal deficits usually associated with damage to the NAC proposes that these impairments do not "stem from a global interference with primary reinforcement or hedonia, but rather can be considered deficits in complex sensory-motor function" (Salamone, 1992, p. 168). In this view, it is possible that the initial disruption to temporal discrimination in the current study may have been related to NAC modulation of brain regions more directly involved in timing such as the SN or the CPu.

Mean response latencies for the NAC lesioned rats tended to be slightly but significantly shorter than sham latencies in the seconds range in Part 2 and shorter response latencies were also found in first post surgery bisection test in Part 1. This may reflect the hyperactivity observed in rats with NMDA lesions compared with dopamine depleting (6-hydroxydopamine, 6-OHDA) lesions to the NAC (Weissenborne & Winn, 1992). This reported dissociation between the effects of NMDA and 6-OHDA lesions on motor activity suggests that the NAC modulates motor behaviour, perhaps through its projections to the SN. These same pathways may also modulate some of the proposed interval timing functions of the nigrostriatal system.

Recent advances have been made in specifying the neural systems that subserve interval timing in rats and humans. The basal ganglia have been clearly implicated and studies with rats suggest that dopaminergic systems in the basal ganglia and cholinergic systems in the frontal cortex are involved in clock and memory stages of temporal information processing, respectively. As reviewed in Section 1.5, Meck (1996, Hinton & Meck, 1997) has recently suggested that the SN is involved in timekeeping through a pacemaker role whereas the CPu subserves switch processes. Accumulation occurs through the internal pallidal segment and this

information is passed to frontal and limbic systems through the thalamus (Meck, 1996, Figure 3, p. 231).

The role of the cerebellum and its interaction with these frontal-thalamic-striatal circuits involved in interval timing is unclear. Gibbon et al (1997) have suggested that cerebellar damage produces tonic deregulation of thalamic function adding noise to the information passing through the thalamus to the frontal systems involved with memory processes in interval timing. This proposal is based on neuroanatomical evidence that pathways from the basal ganglia and the cerebellum pass through the ventro-lateral thalamus in close proximity to converge on common frontal cortical and limbic regions. However, the behavioural evidence following lesions to the cerebellum in the current thesis does not support this proposal and suggests instead that, within the context of the mode-control model, the neural substrates that subserve clock processes rather than memory/comparator processes are disrupted following cerebellar lesions.

There appears to be modest convergence of cerebellar and basal ganglia projections on the ventral medial and parafascicluar nuclei of the thalamus (Denaiu et al, 1996) and through these convergent projections the cerebellum "might contribute to raise the excitability of thalamic cells and in this way increase the efficacy of the disinhibitory mechanism that is used by the basal ganglia to express their function (Denaiu & Chevalier, 1985)" (Denaiu et al, 1996, p. 205). The degenerating terminals found in the SN and evidence of fluctuations in DA levels in both SN and CPu following stimulation of the lateral cerebellar nuclei suggest that the cerebellum may also have a more direct influence on the nigro-striatal system that appears to subserve clock processes.

5.3 Unresolved issues and future research

The issue of cerebellar involvement in the processing of short duration stimuli was only treated indirectly in the current thesis. In this study, there was no relationship found between the brevity of events in number-relevant and time-relevant signals in Part 1 of Experiment 3.1. The possibility that cerebellar damage may impair discrimination of the non-temporal attributes of

short duration stimuli has been addressed by Clarke et al (1996). They found that rats with cerebellar lesions were not impaired in discriminating the amplitude of short durations of sound, although it has been suggested that ease of discrimination may have been an issue due to ceiling effects (Gibbon et al, 1997). Clarke et al (1996) did not report response latencies, so it is not known whether response latencies were longer for cerebellar rats in either the millisecond discrimination or the amplitude discrimination. If longer response latencies were also found with non-temporal discrimination, we could be more confident that the latencies are related to motor deficits rather than cognitive impairment; it might also prove useful to test hemisphere lesioned rats' motor performance in a straight runway.

The current research provided preliminary evidence of a small but relatively permanent increase in constant variance for cerebellar hemisphere lesioned rats. An attempt was made to quantify this impairment (Chapter 4, Part 2) but it appears that much shorter durations than those used in the current study may be required. A staircase procedure such as that used by Killeen & Fetterman (1992) or more extensive bisection testing in the range between 50 and 200 ms should allow the generalised Weber function to be used to accurately estimate constant variance. A more novel approach might be the procedure used by Meck and Church (1983) to establish a quantitative equivalence between time and number. In this procedure, the slope and intercept of the linear function that relates subjective time to the number of segments in a sequence can provide direct estimates of switch closure latency (t_1) and the latency to reopening the switch (t_2, Meck, Church, & Gibbon, 1985, see Section 1.2.2). Meck and Church's (1983; Meck, Church & Gibbon, 1985) finding of a quantitative equivalence between time and number would also be strengthened by independent replication, especially given the results of Experiment 2.1 in the current thesis.

A comparative study between rats and humans with cerebellar damage modelled on the approach adopted by Killeen & Fetterman (1992) to compare interval timing performance between neurologically intact humans and pigeons might be particularly useful in identifying the similarities and differences between rats and humans with cerebellar damage. This type of study might help account for differences that are emerging between interval timing performance in rats (subtle deficits limited to the millisecond range) and humans (some deficits in both the

millisecond and seconds range) with cerebellar damage. Another issue related to differences between humans and rats with cerebellar lesions is that experimental designs for human subjects have tended to involve relatively little training and testing so as to minimise the inconvenience to the subjects. However, given the relatively transient nature of some of the effects found with cerebellar damage in rats, it might be illuminating to investigate the impact of extended training on interval timing performance in humans with cerebellar damage. Furthermore, given the current findings showing an increase in response latency for hemisphere rats, reaction time and the shape of the reaction time function in the bisection procedure with humans may provide some additional insights.

The dissociation between the impact of NAC and cerebellar hemisphere lesions on temporal discrimination in the current study and evidence of basal ganglia involvement in millisecond range timing (Boyle et al, 1996) suggests an alternative, but complementary, approach to the nature of the neural substrates underlying millisecond range timing. If the mode-control model describes an extended timing system responsible for interval timing across millisecond and seconds durations, experimental manipulations that have already been shown to effect interval timing in predictable ways could be applied to millisecond range discriminations. For example, dopaminergic drugs should produce phasic changes in PSE whereas cholinergic drugs should produce chronic changes in PSE in both the millisecond and seconds time range. This approach could also involve microinjection of DA-receptor antagonists into specific sites in the frontal striatal pathways proposed as the neural substrates for the various components of the mode control model (Meck, 1996). For example, if the CPu is involved in switch processes, microinjection of a DA antagonist should increase variability in both millisecond timing and numerical discrimination but have relative little impact on seconds range variability. If the SN serves as the pacemaker, microinjection of DA agonists or antagonists into this brain region should shift the PSE in numerical discrimination and both millisecond and seconds range tasks.

5.4 Conclusions

The current thesis has provided additional evidence of cerebellar involvement in interval timing and some new evidence of cerebellar involvement in numerical discrimination. Overall, there was little support for the view that the cerebellum provides the neural basis for an independent millisecond range interval timer. The current results also clearly conflict with the proposal that cerebellar damage adds scalar variance to an extended interval timing system because overall variance in seconds range timing was either the same or less following cerebellar lesions. The current findings do, however, support the view that cerebellar damage adds constant variance to a distributed neural system described by the mode-control model of timing and counting, possibly through cerebellar modulation of switch processes. The thesis also provided the most convincing evidence to date that rats can in fact count, although they do so only in the absence of more salient cues.

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